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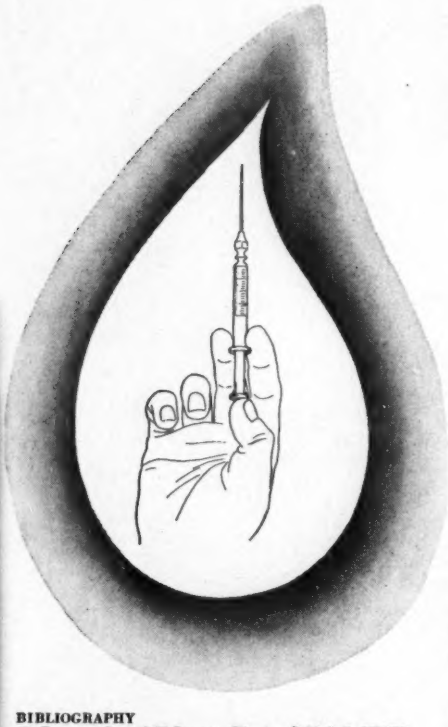

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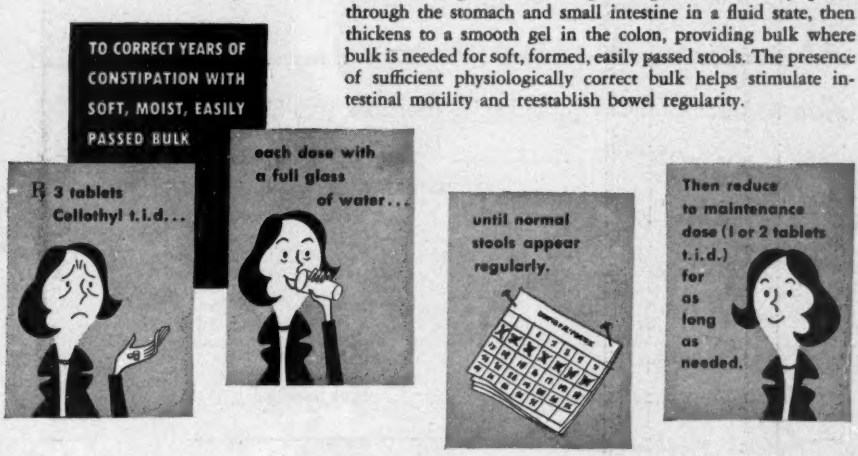
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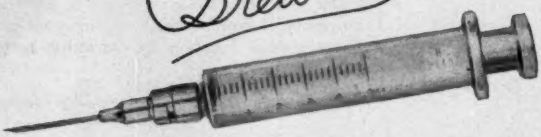

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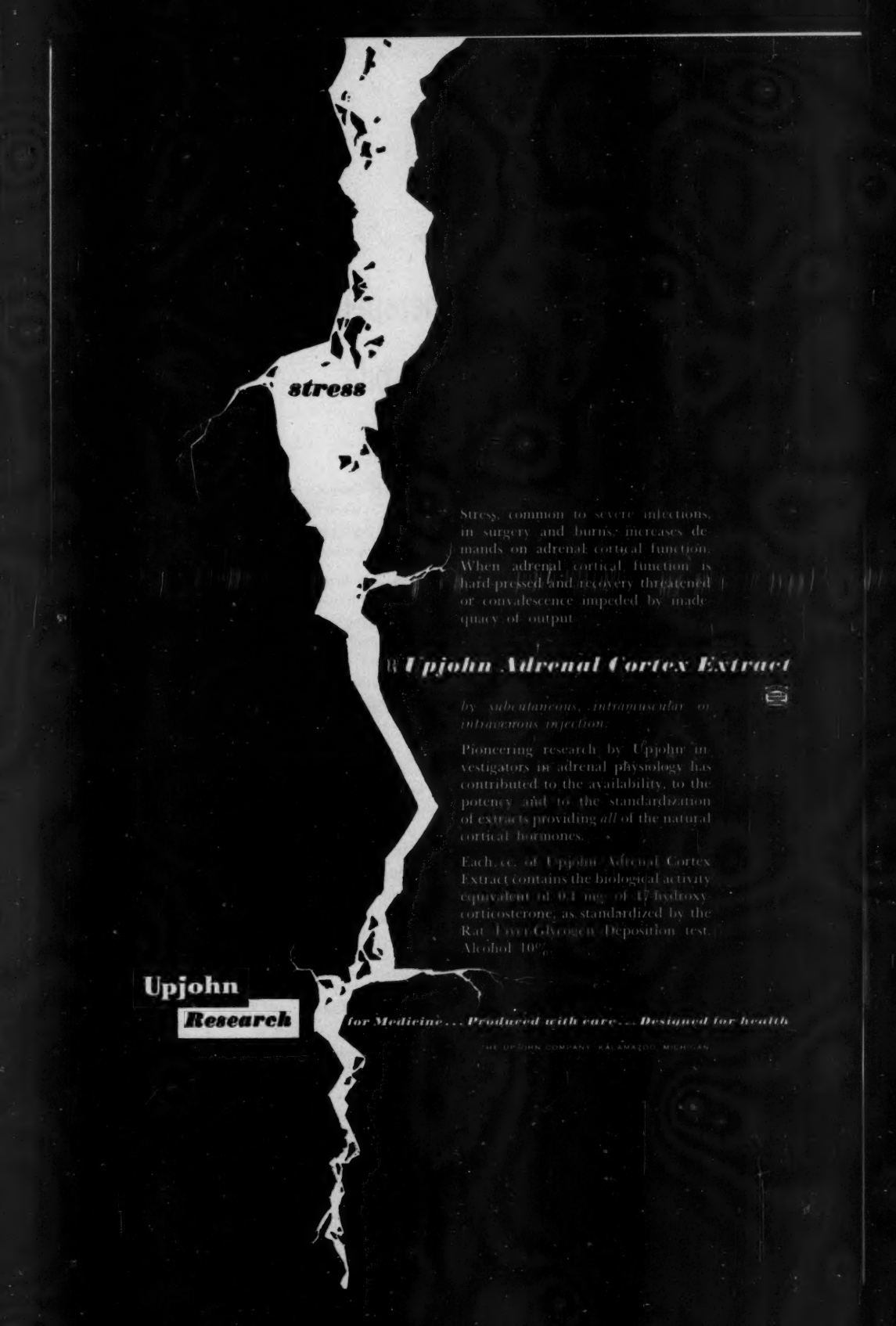

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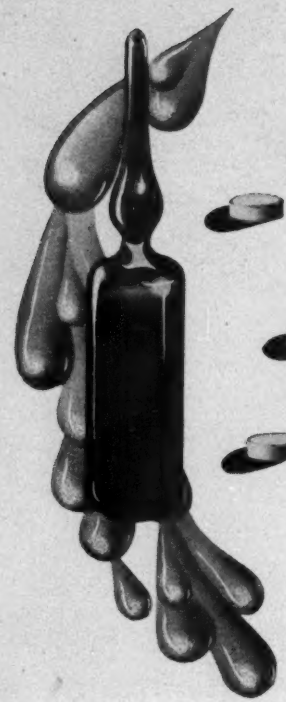

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Methantheline bromide is indicated for clinical use whenever anticholinergic spasmolytic action is desired, provided it is not contraindicated because of its atropine-like characteristics or because of a patient's intolerance to the unavoidable side effects of such therapy. It is useful as an adjunct in the management of peptic ulcer, chronic hypertrophic gastritis, certain less specific forms of gastritis, pylorospasm, hyperemesis gravidarum, biliary dyskinesia, acute and chronic pancreatitis, hypermotility of the small intestine not associated with organic change, ileostomies, spastic colon (mucous colitis, irritable bowel), diverticulitis, ureteral and urinary bladder spasm, hyperhidrosis or control of normal sweating which aggravates certain dermatoses, and control of salivation.

Methantheline bromide produces some degree of cycloplegia and mydriasis in therapeutic doses and therefore should not be administered to patients with glaucoma. It sometimes decreases the ability to read fine print. Xerostomia (dryness of the mouth) is a common, sometimes transient, side effect. Urinary retention of varying degree may occur in elderly male patients with prostatic hypertrophy, and some patients may have difficulty emptying the rectum. Patients with edematous duodenal ulceration may experience nausea and vomiting during initial administration of the drug. These patients should take only liquids during the institution of drug therapy. All patients should be advised of the possible occurrence of side effects. Overdosage sufficient to produce a curare-like action may be counteracted by prompt subcutaneous injection of 2 mg. of neostigmine methylsulfate.

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ARCHIVES OF INTERNAL MEDICINE

VOLUME 88 NOVEMBER 1951 NUMBER 5

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HEMOCHROMATOSIS

Investigation of Twenty-Three Cases, with Special Reference to Etiology, Nutrition, Iron Metabolism, and Studies of Hepatic and Pancreatic Function

T. L. ALTHAUSEN, M.D.
SAN FRANCISCO
R. K. DOIG, M.B.
S. WEIDEN, M.Sc.
R. MOTTERAM, M.B., B.Sc.
C. N. TURNER, B.Sc.
AND
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MELBOURNE, AUSTRALIA

IN THE study of a rare disease it is unusual for one group of investigators to be able to see personally a large series of cases. The occasion of the visit of one of us (T. L. A.) to Melbourne, Australia, was taken to study a group of 15 patients with hemochromatosis (13 men and 2 women) and to assess case records and pathological material available on a further eight patients (7 men and 1 woman). All the patients had been seen at the Clinical Research Unit of the Walter and Eliza Hall Institute and the Royal Melbourne Hospital in the last three and one-half years.

As a basis for this study we took the excellent monograph on hemochromatosis by Sheldon [1] and found that little need be added, on the clinical side, to his description of the disease. But in the last few years advances have taken place in the knowledge of the nutritional causes of hemosiderosis [2]; various new liver function tests have been developed, and a start on the problem of biochemical tests of pancreatic function has been made. Liver biopsy now replaces skin biopsy as the most reliable test for diagnosis, and in the Clinical Research Unit gastric biopsy has been tested out against these two techniques. We have, therefore, sought to make a clinical, nutritional, biochemical, and pathological study of hemochromatosis, with special reference to etiology, to nutrition, to iron metabolism, to tests of hepatic and pancreatic function, and to a study of skin, liver, and gastric biopsy material.

Of the 23 patients, 13 men and 2 women were studied intensively, 3 men and 1 woman could not be seen personally, and 4 men had died.

Read before the Sixty-Third Annual Meeting of the Association of American Physicians, Atlantic City May 3, 1950.

From the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, and the Division of Medicine, University of California School of Medicine, San Francisco.

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2. Gillman, J., and Gillman, T.: Pathogenesis of Cytosiderosis (Hemochromatosis) as Evidenced in Malnourished Africans, Gastroenterology 8:19, 1947.

ETIOLOGICAL FACTORS

Family History.—A history of hemochromatosis was discovered for a brother of one female and of one male patient (Cases 5 and 12). In the brother of the first patient, the diagnosis was based on the presence of diabetes, an enlarged liver, and a positive reaction to the ferric ferrocyanide (Prussian blue) test on the urinary sediment. The brother of the second patient had typical hemochromatosis in the asymptomatic stage. A family history of excessive pigmentation was found in four cases, of diabetes in four, and of hepatic disease in three.

Nutritional Status.—A careful dietary history, covering the adult life of the patient, was obtained by a dietitian (C. N. T.) in 16 cases. The dietary constituents were estimated and compared with those of a control group which consisted of 25 male patients, with social and occupational backgrounds approximately similar to those of our patients with hemochromatosis. In both groups the recommendations of the National Research Council [3] were used as a standard. From Table 1 it is readily seen that for our patients with hemochromatosis the diet was adequate in calories and contained optimum or even higher amounts of protein and of important minerals and vitamins. The distribution of calories among fat, carbohydrate, and

TABLE 1.—*Dietary Intake Expressed as Percentage of Optimum Amounts Recommended by the National Research Council of America* [3]

	Total Calories	% of Total Calories			Protein, % of Optimum	Calcium	Phosphate	Iron	Vitamin A	Thiamine	Riboflavin	Nicotinic Acid	Ascorbic Acid
		Carbohydrate	Fat	Protein									
Controls (25 men)	109*	48	39	13	165	112	129	145	149	89	148	133	130
	56-160†	36-58	30-54	10-20	111-228	12-227	70-222	92-225	56-306	48-134	74-319	69-191	59-333
Hemochromatosis (14 male patients)	124*	44	43	14	207	104	138	175	201	98	142	162	98
	77-178†	22-61	30-55	9-23	100-650	40-329	67-275	95-423	78-407	69-145	64-310	79-428	58-144

* Average.
† Range.

protein showed only minor differences in the two groups. The diet of the two women with hemochromatosis was an exception, since their intake of some minerals and vitamins was slightly deficient.

The weight of the patients at the onset of the symptoms (exclusive of pigmentation and hepatomegaly) varied considerably in both directions from the ideal weight,[4] so that the average showed no consistent change. A similar variation was observed in the control group. After the clinical onset of the disease and the stabilization of diabetes when present, a weight deficit averaging 8 kg. was observed, but again the range was wide—from + 24 to — 32 kg.

There was evidence that the intake of alcohol by 10 of 20 patients for whom information on this point was obtained was excessive. Of 16 patients whose diets were studied in detail, the intake of alcohol was high for six and moderate for four. In the other six it was slight or nil. No difference in clinical findings existed among these three groups, so that alcoholism cannot be the sole factor in the development of the disease. By the time the patients' conditions were diagnosed and they came under

3. Recommended Dietary Allowances, Revised 1948, National Research Council Reprint and Circular Series No. 129, Food and Nutrition Board, National Research Council, Washington, D. C., 1948.

4. Average Weights for Australians, Food and Nutritional Notes and Reviews of the Australian Institute of Anatomy, 1949, Vol. 6.

observation they had almost all ceased to drink or drank very little. Patient 23 and, according to a close relative, Patient 19 were exceptions; in these patients chronic alcoholism interfered with the partaking of adequate meals.

Iron Metabolism.—The dietary intake of iron by our patients with hemochromatosis and by the control group exceeded somewhat the optimum, as recommended by the National Research Council, but by amounts relatively much less than those employed by Hegsted and associates,[5] who produced increased iron absorption in experimental animals. Phosphates were in normal amount, so that a lowered content of this radical as a cause of increased absorption of iron was ruled out. The same authors [5] showed that gross diminution of phosphates in the diet will increase iron absorption in rats.

The average level of iron in the serum of 18 patients with hemochromatosis was almost 80% higher than the average normal figure of 143 γ for men, as obtained by Powell.[6] Twelve of these patients had levels of serum iron exceeding the upper limit of normal, and in four patients very high levels, between 360 and 480 γ, were found (Table 2). In five cases the serum iron determinations were repeated after an average interval of 15 months. In each case a marked increase was observed.

In several patients with cirrhosis of the liver, we also observed an increased iron content of the serum ranging from 180 to 230 γ per 100 cc. A similar observation was reported by Howard [7] in "nonalcoholic" types of hepatic cirrhosis.

The average hemoglobin concentration for our group of 22 patients was normal (14.5 gm. per 100 cc.); only 2 patients had a hemoglobin concentration slightly below the normal limits. The blood counts were within normal limits in all cases.

In our three female patients the menstrual history was abnormal, so that considerably less blood was lost during the reproductive period. The periods of one patient (Case 5) were scanty and lasted only one and one-half days, the duration of the cycle varied and was often greater than four weeks, and frequently periods were missed. She had no children. Menstruation of the second patient (Case 7) was normal, but the loss was for two days only. She had one child. The third patient (Case 19) experienced early cessation of menstruation at 29 years. This patient also had only one child. One of the problems in hemochromatosis is the rarity of the disease in females. It has been suggested that the loss of iron which normally occurs with menstruation and childbirth prevents the appearance of hemosiderosis in women. In each of our patients there was some extraneous factor reducing this loss and thus permitting hemosiderosis to develop.

Toxic Factors.—On close questioning of 15 patients, no evidence was found to suggest that toxic factors are important in the production of hemochromatosis.

CLINICAL FEATURES

The accepted picture of hemochromatosis is that of a disease characterized by pigmentation of the skin, hepatomegaly, weakness, and frequently, diabetes, to which may be added diminution in sexual activity, testicular atrophy, and relative lack of body hair in males. Except in Patient 1, these features were present in varying

5. Hegsted, D. M.; Finch, C. A., and Kinney, T. D.: The Influence of Diet on Iron Absorption: The Interrelation of Iron and Phosphorus, J. Exper. Med. **90**:147, 1949.

6. Powell, J. F.: Serum-Iron in Health and Disease, Quart. J. Med. **13**:19, 1944.

7. Howard, R. B.: The Serum Iron in Diseases of the Liver, J. Clin. Invest. **29**:324, 1950.

TABLE 2.—*Summary of Clinical Features in Patients with Hemochromatosis**

Case No.	Sex	Age, Yr.	Onset; Symptoms, and Duration	Period of Observation	Diabetes†	Weakness	Changes in Body Hair and Genitalia‡	Hepatomegaly, Cm.	Serum Iron, γ	Date	Comment
1	M	29	Fatigue, lack of energy 6 mo.; sweats 1 mo. due to brucellosis	2 mo.	+	2+	A	0	460	10/49	Brucellosis: liver biopsy specimen showed typical granulomas plus extensive hemosiderosis
2	M	49	Weakness and pigmentation 25 yr.	8 yr.	0	3+	B	8	178 186 240	1/48 9/49 10/49	Empyema 1940; cough and sputum since; had duodenal ulcer which bled; originally diagnosed as Addison's disease
3	M	37	Severe backaches and muscle cramps 17 yr.	18 mo.	0	3+	A	6	118 460	3/48 10/49	.....
4	M	54	Crop of boils 9 yr. ago; onset of diabetes 8 yr. ago	6 mo.	++	2+	D	4	145	10/49	Hypertension; Bright's disease at age 15
5	F	64	Abdominal pain and poor general health 30 yr.	18 mo.	+	3+	..	6	261 360	4/48 10/49	Barium sulfate meal normal twice; recently 2 gastric ulcers seen; brother died of hemochromatosis
6	M	46	Vague abdominal ache 4-5 yr.; thirst, loss of weight, glycosuria 6 wk.	6 mo.	++	2+	C	8	134	10/49	Question of duodenal ulcer by x-ray 2 yr. ago; transient ascites; diabetes difficult to stabilize; died Jan., 1951, in hepatic coma precipitated by severe melena
7	F	58	Cramps in legs and toes due to diabetes 12 yr. ago	14 mo.	++	3+	..	8	285	10/49	Has hypertension, diabetic retinitis, cholelithiasis, atrophic gastritis, and persistent diarrhea; thyroidectomy 13 yr. ago; no hemosiderin in section
8	M	57	Symptoms of diabetes 3 wk.	3 yr.	++	3+	D	6	120	10/49	.....
9	M	58	Melena 1 yr. before admission; hematemesis 2 days before admission	20 mo.	+	3+	D	8	110	11/49	Lump on liver 27 yr. ago; gastrointestinal series after hematemesis "difficulty in filling of pyloroduodenal area"; had extensive spider nevi; ECG: right bundle branch block; died April, 1951, of hematemesis from esophageal varices
10	M	49	Lack of energy 6 mo.; thirst 3 mo.; persistent loss of weight; diabetes	2 yr.	++	2+	B	8	200	10/49	No liver biopsy; skin biopsy suggestive; clinically typical case
11	M	44	Weakness 2 yr.	8 mo.	+	2+	A	8	223 300	2/49 10/49	Has bilateral congenital cataracts and macular degeneration; partly deaf; told he had "liver trouble" many years ago
12	M	42	Cough and sputum 3 wk.; hematemesis just prior to admission	16 mo.	0	±	D	3	270	10/49	Gastrointestinal series normal; pneumonia slow to resolve; some residual fibrosis in right upper lobe; pigmentation faded partly under treatment; a brother has hemochromatosis

13	M	57	Dyspnea on exertion and edema 2 yr.; in hospital, pigmentation noted and diagnosis made	21 mo.	+	±	A	0	220	10/49	Hypertension; overweight; receiving digitalis; ECG: auricular fibrillation and right axis deviation
14	M	62	Thirst, polyuria, loss of weight 3 mo.	3 yr.	++	2+	B	4	380	10/49	Dyspnea on exertion; ECG suggests myocardial damage
15	M	60	Precordial pain 17 yr.; dyspnea and edema 6 mo.; diagnosed because of enlarged hard liver	3 mo.	+	±	B	6	210	10/49	Liver known to be enlarged in 1933; hypertension; senile cataracts
16	M	55	Lassitude 3 yr.; boils after pneumonia; diabetes 5 wk.	4 mo.	++	2+	..	8	189	9/49	Liver known to have been enlarged in 1938; hypertension
17	M	62	Weakness and congestive cardiac failure 6 mo.	3 yr.	+	3+	B	6	...	.....	Had ECG changes suggestive of myocardial ischemia and mild cardiac failure; unable to trace
18	M	50	Increasing weakness and lack of energy 7 yr.; swelling of legs and abdomen 7 wk.	4 mo.	0	2+	B	6	184	7/49	Initial diagnosis Addison's disease; ascites and edema may have been due to medication with cortin
19	F	47	Progressive weakness over 6 mo.	3 yr.	0	3+	..	17	...	.....	Chronic alcoholic; repeated severe epistaxis with low prothrombin time
20	M	58	Swelling of abdomen and ankles, dyspnea 5 mo. before death	4 mo.	+	3+	..	4	...	.....	Rheumatic heart disease with auricular fibrillation, probably chief factor in death
21	M	51	Feeling poorly, abdominal discomfort 7 yr. before death	7 yr.	+	2+	D	8	...	.....	Hematemesis in 1945, 1947, and 1948; adenoma of liver at postmortem examination; ascites; not recorded whether pubic hair of female distribution
22	M	60	Thirst, polyuria, loss of weight 5 mo.	4 mo.	++	3+	..	7	...	.....	Ascites; hypertension; downhill course and death
23	M	55	Weakness, loss of weight 9 yr. before admission	3 mo.	+	3+	..	8	178 227	11/49 12/49	Hypertension; died suddenly, probably of cerebral thrombosis; full dietary history obtained

* The first 15 patients were studied thoroughly.

† Under "Diabetes" 0 indicates no hyperglycemia; +, high fasting blood sugar or diabetic dextrose tolerance curve; ++, the same, plus symptoms of diabetes and need for insulin.

‡ Under "Changes in Body Hair and Genitalia" A indicates no change; B, sparsity of axillary and chest hair; C, sparsity, plus female distribution of pubic hair; D, sparsity, plus female distribution, plus atrophic testes.

degrees in all our patients and are summarized in Table 2. Patient 1 with brucellosis is included in the series on the grounds of extensive hemosiderosis in the liver and a high serum iron level, because infection without anemia usually results in a low serum iron value, as described by Cartwright and others.[8]

The modes of onset fell into the following categories (Table 2): In nine cases abnormal weakness occurred; in six symptoms of diabetes; in two abdominal pain; in two hematemesis; in one ascites, and in three the diagnosis was made incidentally during a stay in the hospital for some other reason. In two cases in the last group, the patient was hospitalized because of congestive cardiac failure. Pigmentation as a symptom of onset has been excluded from this tabulation, since in many instances the patients did not realize that they were pigmented or stated that they had been pigmented for as long as they could remember. Further, there was often a history of the incidental finding of enlargement of the liver several years previously; this finding has also been left out in this consideration of onset. Excluding Patient 1 (aged 29 years), the ages of the patients ranged from 37 to 64 years.

In 18 patients the skin was noticed to be of fine texture and shiny or thin and dry—both states indicating the atrophy seen on the biopsy specimen. In all but one patient the typical bluish-gray pigmentation was present. In most patients there was also an extensive brown pigmentation which involved a greater area than the gray pigmentation. Both types were most prominent on the face, neck, arms, and legs. Six patients were pigmented all over, but more deeply on the parts mentioned. The bluish-gray color was observed in purest form on the medial or flexor aspects of the forearms. In 4 of 15 patients there was brown pigmentation of the mucous membrane of the mouth and lips.

Weakness, easy fatigability, and lack of energy were prominent symptoms of the disease. These were present in 20 of the 23 patients, severely in 12 and moderately in 8. In addition, four patients complained of apathy and two were somnolent. Even after the diabetes was treated with diet and insulin, it was often observed that the patient did not have the energy of the ordinary stabilized diabetic of the same age and occupation.

Nine of the 13 men stated that about the time of the onset of the disease their libido had undergone a premature or abrupt decline. Four patients said that the libido had remained normal. Of 20 male patients, 8 had normal genitalia, 8 had soft or small testes, and 4 had a small penis and atrophic testes. Changes in the body hair of these patients was one of the most striking features of the physical examination. In 10 of 17 patients there was virtually no body hair, except for the pubic hair, and in half of the patients the latter was of typical feminine distribution. The few hairs possessed by these patients were soft and thin. In three more patients, there was a moderate reduction in body hair, and only four were normal in this respect. In addition, of 13 men questioned about shaving, 4 found it necessary to shave every second day, 2, twice a week, and 1, once a week. Similar observations have been made on patients suffering from portal cirrhosis and have been attributed to a "feminization" associated with the disease. One of us (T. L. A.) has called attention to the fact that these patients with cirrhosis will regularly report that such

8. Cartwright, G. E.; Lauritsen, M. A.; Jones, P. J.; Merrill, I. M., and Wintrobe, M. M.: Anemia of Infection: Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients, J. Clin. Invest. **25**:65, 1946.

features have been present for as long as they can remember. In the present investigation the same history was obtained. None of the patients would admit that there had been any change in the hair.

In the majority of patients a history of dyspnea on exertion or of edema of the ankles was obtained, but it was difficult to separate dyspnea caused by weakness from that caused by cardiac failure. Two patients were first admitted to the hospital because of hypertensive heart failure with fibrillation (Cases 13 and 15), and the first admission of a third was because of rheumatic heart disease with fibrillation (Case 20). Four other patients had hypertension with mild dyspnea or edema, and another had hypertension without any symptoms of cardiac failure. In two further patients (Cases 14 and 17), mild cardiac failure was accompanied with electrocardiographic changes suggestive of myocardial damage. Electrocardiograms in three other patients showed low voltages; in one patient there was right-bundle-branch block, and in seven (including three patients with hypertension) the electrocardiographic patterns were normal.

A history of indigestion was obtained from 12 patients. In two it was shown to be due to peptic ulcer, but more usually its character was not specific.

THE LIVER

The liver obviously plays an important part in hemochromatosis. In his monograph Sheldon [1] discussed at length the clinical and pathological features of hepatic cirrhosis in hemochromatosis. However, he reported few attempts to estimate the functional efficiency of the liver, and these attempts were made mostly with liver function tests that are no longer in use. Papers on hemochromatosis which appeared after the publication of Sheldon's monograph have added little to the knowledge of the functional efficiency of the liver in this disease. Hence, one of the major aims of this investigation was a survey of the various functions of the liver by the newer laboratory methods.

Clinical Findings.—On physical examination the liver was found to be palpable, or a suggestive resistance was felt, in all patients except Patient 1. In 13 patients it was enlarged to 8 cm. or more below the costal margin. Three patients (Cases 9, 14, and 16) had a single large mass projecting from the surface of the liver; in two patients the mass was certainly benign, and in the third almost as certainly benign, on the score of passage of time since the discovery of the mass. In Patient 21 an adenoma of the liver was observed at autopsy. The spleen was felt definitely in six patients and questionably in one.

The following complications of hepatic cirrhosis were present: ascites in five patients (Cases 18, 20, 21, 22, and transiently in Case 6), enlargement of superficial abdominal veins in three patients (slight in Cases 2 and 9 and severe in Case 21), and hematemesis in three patients (Cases 9, 12, and 21). In one of the last patients the hematemesis was shown at autopsy to have been due to esophageal varices, but in the other two it is doubtful whether portal hypertension was the cause of the bleeding. Less direct effects of hepatic cirrhosis were subcutaneous ecchymoses in four patients and spider nevi in five.

Biochemical Investigations.—Numerous biochemical tests which are considered to reflect various phases of hepatic function were carried out on our patients, and especially in the group studied extensively. Of the 23 patients examined, 7 had a

slightly raised serum bilirubin level, 7, a moderately elevated serum alkaline phosphatase, and 3, a prolonged prothrombin time. In the urine the urobilinogen was slightly raised in 2 of 20 patients, while bilirubin and bile salts were found in 3 and 4 patients, respectively, of the 16 tested. The total serum albumin of seven patients was less than 4 gm. per 100 cc., and of these only one (Case 20) showed a reversed albumin-globulin ratio.

The results of the more sensitive liver function tests [9] are shown in Table 3. A significantly positive cephalin flocculation was obtained in only one of the special group of 15 patients studied. In three others the result of the test was 1 +. Thymol turbidity reactions of between 5 and 8 units were considered as slightly abnormal, and those above 8 units, as definitely abnormal. On this basis the thymol turbidity was definitely high in four patients and slightly abnormal in eight. The thymol flocculation reaction was negative in all instances. The gamma globulin, estimated by means of the zinc sulfate turbidity, was increased in 8 of 15 patients.

TABLE 3.—*Results of Liver Function Tests of Fifteen Patients with Hemochromatosis Studied in Detail*

Case No.	Cephalin Flocculation	Thymol		Gamma Globulin, Gm./100 Cc.	Serum Albumin, Gm./100 Cc.	Hippuric Acid Synthesis, Gm.	Sulfobromophthalein Retention, 45 Min., %	Liver Biopsy Specimen
		Flocculation	Turbidity, Units					
1	0	0	6	1.08	5.5	0.42	10	Hemosiderin only
2	0	0	4.6	1.05	4.8	0.82	5	Hemosiderin only
3	0	0	5	1.30	5.2	0.72	5	Multinodular cirrhosis
4	0	0	3.5	1.08	4.7	0.22	5	Multinodular cirrhosis
5	0	0	5.5	1.26	4.0	0.59	5	Hemosiderin only
6	++	0	12.5	1.22	3.9	0.42	20	Multinodular cirrhosis
7	+	0	8	1.43	4.3	0.23	10	Multinodular cirrhosis
8	0	0	7	1.35	6.4	0.20	10	Multinodular cirrhosis
9	0	0	7	1.30	3.9	0.79	20	Multinodular cirrhosis
10	0	0	5.2	....	4.0	0.80	7	No biopsy
11	+	0	8.6	1.12	6.2	0.97	..	Multinodular cirrhosis
12	0	0	7.3	1.21	6.2	0.22	5	Laennec cirrhosis
13	0	0	9.5	1.49	4.8	0.33	15	Laennec cirrhosis
14	0	0	6.5	1.13	5.2	0.39	5	Multinodular cirrhosis
15	+	0	9.0	1.52	4.3	0.29	5	Multinodular cirrhosis
Normal	0 to +	0	<5	<1.24	>4	>0.7	<5	

The test with intravenous administration of hippuric acid was used in 15 cases and in 10 gave values below normal. Previous oral hippuric acid tests disclosed abnormally low values for all of seven patients. The test with sulfobromophthalein (bromsulphalein®) sodium showed abnormal retention of dye by 7 of 14 patients.

Of the eight patients not seen personally, results of cephalin flocculation tests were negative for three, 1 + for two, 2 + for one, and 4 + for one. In six of these seven patients the synthesis of hippuric acid after oral administration of sodium benzoate was greatly reduced.

A review of the results of these liver function tests reveals that the reactions to the intravenous hippuric acid test and the gamma globulin determinations showed impaired function in two-thirds of the patients. The sulfobromophthalein excretion was reduced in just less than one-half of the patients, and the thymol turbidity reaction was positive in less than one-third of the cases. Surprisingly, the cephalin

9. Mateer, J. G.; Baltz, J. I.; Steele, H. H.; Brouwer, S. W., and Colvert, J. R.: Chronic Subclinical Impairment of the Liver: Early Diagnosis and Treatment; Further Improvement and Evaluation of Certain Liver Function Tests, J. A. M. A. **133**:909 (March 29) 1947.

flocculation was abnormal for only one patient of the group specially studied and for two patients who died before this study was undertaken. The serum albumin was reduced slightly (3.9 gm. per 100 cc.) in two patients of the special group and moderately (3.1 to 3.8 gm. per 100 cc.) in five patients of the additional group, four of whom had died.

There was considerable correlation among the positive results shown by the four liver function tests which were most sensitive to the hepatic changes in hemochromatosis. As would be expected, the degree of correlation was roughly in inverse proportion to the frequency of positive results. Nearly one-half of the patients with a positive reaction to the hippuric acid test had both abnormally high gamma globulin and pathological retention of sulfobromophthalein. One-half of the patients with high gamma globulin had both low hippuric acid synthesis and abnormal retention of sulfobromophthalein. Three-fourths of the patients with pathological retention of sulfobromophthalein or high values on the thymol turbidity test had both abnormally high gamma globulin and low synthesis of hippuric acid.

There was also a fair degree of correlation between the results of the liver function tests and the results of histopathological examination of biopsy specimens, even though the biopsies on these patients were performed somewhat earlier than the special study of hepatic function. Among three patients whose biopsy specimens showed only a small increase in connective tissue, two patients with large deposits of hemosiderin in the liver had entirely normal hepatic function by all tests. In all 11 patients whose biopsy specimens revealed a picture of hepatic cirrhosis, regardless of type, results were positive on one to six of the liver function tests detailed in Table 3.

From this analysis it can be concluded that a moderate impairment of hepatic function is usually present in hemochromatosis by the time cirrhotic changes can be demonstrated histologically. Further, negative findings on liver function tests do not rule out the presence of hemochromatosis in the precirrhotic stage. Marked impairment of hepatic function recorded in several liver function tests usually indicates the presence of aggravating factors or the terminal stage of the disease.

THE PANCREAS

Diabetes in hemochromatosis depends on organic changes in the pancreas, as shown by autopsy material. Most important of these changes are fibrosis and a diminution in number, or even disappearance, of the islands of Langerhans. The degree of pigmentation of the islands has no consistent relation to the diabetic state.[1]

In our group of 23 patients diabetes was present in 18 (Table 2). Nine patients had characteristic symptoms of the disease and required insulin administration to prevent glycosuria. In the other nine, the presence of diabetes was manifested only by a high level of the fasting blood sugar or by a diabetic dextrose tolerance curve. Our patients with diabetes showed no undue tendency to acidosis, and in only one was there any difficulty in stabilization with diet and insulin. When the diabetes with hemochromatosis was first treated with insulin, great difficulties in stabilizing the patients were encountered by several clinicians, including one of us (T. L. A.).[10]

10. Althausen, T. L., and Kerr, W. J.: Hemochromatosis: (*a*) I. A Report of Three Cases with Results of Insulin Therapy in One Case, Endocrinology **2**:377, 1927; (*b*) II. A Report of 3 Cases with Endocrine Disturbances and Notes on a Previously Reported Case: Discussion of Etiology, ibid. **17**:621, 1933.

As a result, the opinion prevailed that patients with hemochromatosis are resistant to insulin. This opinion is no longer tenable in the light of present knowledge, as indicated, among others, by King and Downie.[11] The daily insulin requirements of nine patients ranged from 12 to 86 units.

Sheldon stated that pancreatic fibrosis occurred in 90% of patients with hemochromatosis. In spite of this report, studies of the exocrine function of the pancreas in this disease have received scant attention. This may be owing largely to the lack of simple methods and the difficulty in separating digestive from absorptive functions of the alimentary canal. In this investigation we, therefore, set out to study pancreatic function in hemochromatosis.

In recent years advances have been made in the development of biochemical tests for pancreatic function. Anfanger and Heavenrich[12] studied the rate of absorption of whole protein as compared with that of partially hydrolyzed protein and amino acids in children with cystic fibrosis of the pancreas, the celiac syndrome, and other

TABLE 4.—*Studies of Pancreatic Function in Hemochromatosis*

Case No.	Rise in Amino Nitrogen of Blood, Mg./100 Cc.		Duodenal Contents After Secretin		
	After Gelatin	After Glycine	Volume, Cc.	Bicarbonate Concentration, mM./Cc.	Total Bicarbonate, mM.
1	3.6	3.8	107	0.110	11.7
3	2.7	...	350	0.060	21.1
4	2.2	6.4	187	0.038	6.4
5	6.3	...	...	.....	....
6	1.7	3.4	...	.....	....
7	3.7	..	...	.....	....
8	4.1	..	223	0.064	14.4
9	3.5	...	...	.....	....
11	2.0	...	...	.....	....
12	0.5	3.2	333	0.072	24.8
13	0.9	4.1	166	0.093	15.4
14	1.6	3.0	480	0.052	25.4
15	1.8	4.6	...	.....	....
Normal range	2.0	2.5	90-192	72-128	10.7-17.75

conditions. They found that after a dose of gelatin taken orally the amino nitrogen level of the blood rose in all patients, except those with cystic fibrosis of the pancreas. The rise was ascribed to failure of pancreatic digestion of the gelatin. In those patients in whom no rise was obtained, the amino nitrogen level was measured after ingestion of glycine to rule out the possibility of faulty intestinal absorption of amino acids.

It was decided to carry out these two tests on our patients with hemochromatosis. At the same time, a control group of six patients without pancreatic disease was also studied in order to establish values for normal adults. In the normal patients a dose of 50 gm. of gelatin produced a rise in the amino nitrogen in the blood of between 2.1 and 5.9 mg. per 100 cc.; the same amount of glycine caused a rise of 2.5 to 8.3 mg. per 100 cc. From these results it seemed that a rise of less than 2 mg. per 100 cc. may be considered as abnormal. Five of the 13 patients with hemochromatosis

11. King, W. E., and Downie, F.: Haemochromatosis: Observations on the Incidence and on the Value of Liver Biopsy in Diagnosis, Quart. J. Med. **17**:247, 1948.

12. Anfanger, H., and Heavenrich, R. M.: Amino Acid Tolerance Tests in Children, Am. J. Dis. Child. **77**:425 (April) 1949.

subjected to this test had values below this level after ingestion of gelatin but showed a normal rise after taking glycine (Cases 6, 12, 13, 14, and 15; Table 4). These results suggest that in these patients there was an impairment of the ability to break down gelatin, probably due to insufficient secretion of trypsin. The outcome of this test bore no relation to loss of weight or to caloric intake in our patients. The lack of such correlation, however, may be explained by a compensatory prolongation of digestion and absorption in the small intestine, as pointed out by one of us in another connection (T. L. A.).[13]

The other test used by us for detecting insufficiency of the internal secretion of the pancreas was measurement and analysis of the duodenal contents before and after stimulation by secretin, according to the method of Dornberger and co-workers.[14] In this test duodenal secretions were collected at 10-minute intervals. After two control specimens were taken, secretin[15] was injected intravenously in doses of 1 unit per kilogram of body weight; then four further specimens were collected. The volume and bicarbonate secretion of each collection were determined. From these figures the total bicarbonate excretion after stimulation with secretin was calculated. Dornberger and his co-workers found that in a group of 20 normal subjects the average volume secreted in 40 minutes after stimulation with secretin was 122.5 cc. (range, 90 to 192 cc.), that the average bicarbonate concentration was 0.105 mM. per cubic centimeter (range, 0.072 to 0.128 mM.), and that the total bicarbonate was 14.8 mM. (range, 10.70 to 17.75 mM.). In all, seven of our patients with hemochromatosis were so studied. The total volume secreted in the 40 minutes after secretin stimulation was abnormally large in four instances (Table 4). The bicarbonate concentration per cubic centimeter was low in four cases. Patient 4 was the only one to secrete a lowered total amount of bicarbonate, 6.4 mM., as compared with the normal average value of 14.8 mM. given by Dornberger.

In the examination of feces, fat globules were seen in specimens from one patient and muscle fibers in those from three patients; the remainder of the specimens were normal. Thus, the results of the stool examinations do not seem to be of significance.

BIOPSIES OF THE LIVER, SKIN, AND GASTRIC MUCOSA

Biopsy material was available from the liver (21 cases), the skin (13 cases), and the gastric mucosa (11 cases). Biopsy of the liver was performed with a Franseen needle by the lateral approach,[16] while biopsy of the gastric mucosa was executed by a method of blind suction recently described by Wood and others.[17]

Excessive accumulation of hemosiderin in the body from any cause becomes manifest first in the hepatic parenchymal cell (Fig. *A*). Therefore, examination of the liver provides a definite criterion for establishing a diagnosis of hemochroma-

13. Althausen, T. L.; Uyeyama, K., and Simpson, R. G.: Digestion and Absorption After Massive Resection of the Small Intestine, Gastroenterology **12**:795, 1949.

14. Dornberger, G. R.; Comfort, M. W.; Wollaeger, E. E., and Power, M. H.: Pancreatic Function as Measured by Analysis of Duodenal Contents Before and After Stimulation by Secretin, Gastroenterology **11**:701, 1948.

15. The secretin used in these studies was manufactured by Wyeth, Inc., Philadelphia 3.

16. King, W. E., and Perry, J. W.: Technique of Aspiration Biopsy of the Liver with Reference to Its Use in Diagnosis and Prognosis, M. J. Australia **1**:697, 1948.

17. Wood, I. J.; Doig, R. K.; Motteram, R., and Hughes, A.: Gastric Biopsy: Report on 55 Biopsies Using a New Flexible Gastric Biopsy Tube, Lancet **1**:18, 1949.

tosis.[18] In three cases (1, 2, and 5) the general hepatic structure was normal, with only a small increase in portal connective tissue. In these cases the hemosiderin content of the parenchymal cells was quite dense, with a tendency to accumulate at the periphery of the lobules.

In four cases (12, 13, 16, and 19) there was a Laennec type of portal cirrhosis, with intersection of lobules by fibrous tissue bands. In Case 13, there was less hemosiderin and fat vacuoles were present in the parenchymal cells. Active fibroblastic proliferation and numerous macrophages suggested an active nutritional hepatitis. Specimens from the other three cases showed a light patchy distribution of hemosiderin in the parenchyma, but large clumps of this pigment were present in the Kupffer cells. No active hepatitis was seen. In all four cases there was a history of excessive use of alcohol.

In specimens from the remaining 14 cases the normal trabecular architecture was completely disrupted, and the appearance was that of a multinodular cirrhosis (Fig. *A*). The fibrous tissue was mature with abundant collagen, and in no case was there evidence either of necrosis or of recent active regeneration of hepatic cells. These observations suggest that the cirrhosis was of long standing, and histologically it appeared to be relatively quiescent at the time of examination of the patients. Hemosiderin was present in gross amounts in the parenchymal cells and in the epithelium of the numerous small bile ducts scattered throughout the fibrous bands.

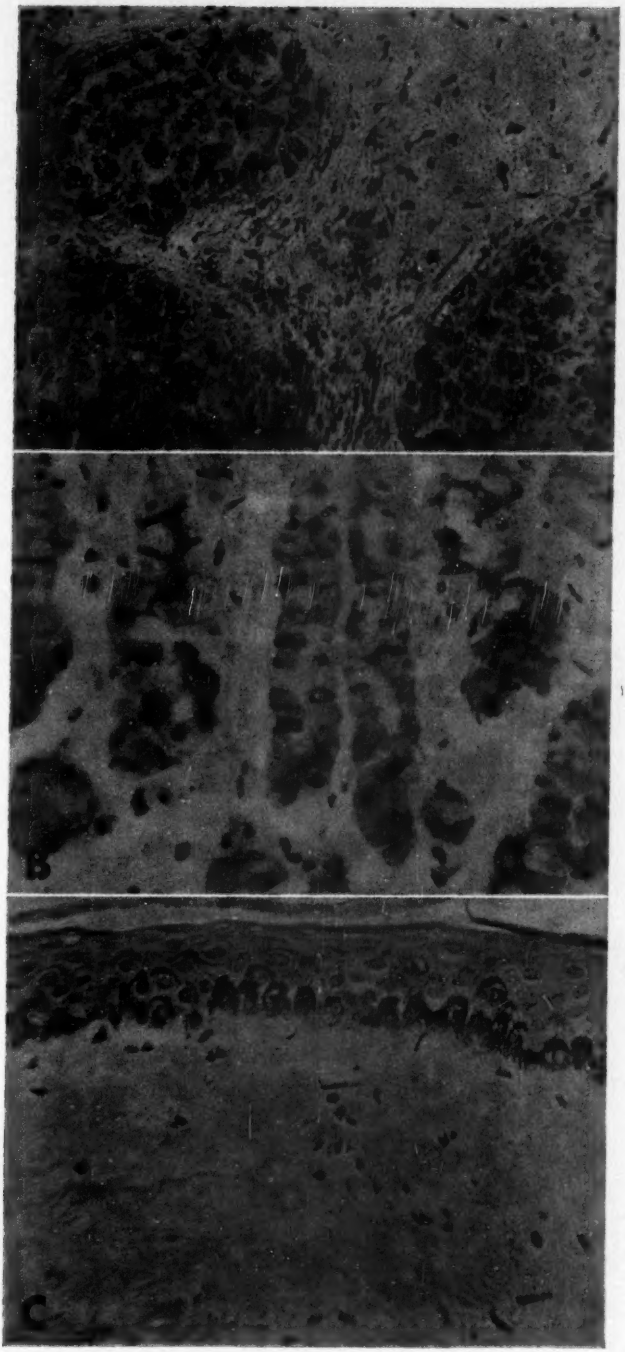
With excessive accumulation of hemosiderin in the body, such as is found in cases of hemochromatosis by the time they are diagnosed, the pigment can be detected in serous secreting cells, such as the pancreatic acini, serous portions of the salivary glands, and the chief cells of the gastric mucosa. In the 11 patients upon whom gastric biopsy was performed, hemosiderin could be demonstrated in every instance (Fig. *B*). There was a rough correlation between the intensity of pigmentation in the liver and that in the gastric mucosa.

In nine patients the gastric mucosa, except for the presence of hemosiderin granules, was normal, and test meals after histamine administration gave normal values for free hydrochloric acid, while pepsin secretion was also normal or slightly lowered. In two cases there was some atrophy of chief and parietal cells, with lowering of the secretion of acid and of pepsin. These findings indicate that the secretory activity of the gastric glands in hemochromatosis corresponds to the histological appearance of the mucosa, as described by Wood and associates,[19] and that the presence of hemosiderin has little or no effect.

The gross appearance of the skin was one of dryness and thinning, with conspicuous lack of hair. The microscopic study showed an atrophy of epidermis and also of hair and sebaceous glands (Fig. *C*). The epidermis was sometimes reduced to a flattened sheet, some four or five cells thick, with a flattening of interpapillary processes. We were unable to demonstrate hemosiderin in the epidermis, but the melanin content of the cells in the basal layers was consistently increased, sometimes to a gross degree. It appears, thus, that the increase in melanin was responsible for

18. King and Downie.[11] Topp, J. H., and Lindert, M. C. F.: The Diagnosis of Hemochromatosis by Means of Needle Biopsy of the Liver, Gastroenterology **10**:813, 1948.

19. Wood, I. J.; Doig, R. K.; Motteram, R.; Weiden, S., and Moore, A.: The Relationship Between the Secretions of the Gastric Mucosa and Its Morphology as Shown by Biopsy Specimens, Gastroenterology **12**:949, 1949.



A (Case 18), liver biopsy specimen showing nodular cirrhosis. Abundant fibrous tissue surrounds many small bile ducts. Inflammatory wandering cells are completely absent. Hepatic cells and bile duct epithelium contain large amounts of blue-staining hemosiderin (ferric ferrocyanide [Prussian blue] and hematoxylin; × 140). *B* (Case 4), biopsy specimen of gastric mucosa. Chief cells of tubular glands are laden with hemosiderin, while the parietal cells are practically free of this pigment (ferric ferrocyanide and hematoxylin; × 450). *C* (Case 2), biopsy specimen of skin showing thinning of epidermis, with flattening of interpapillary processes. Basal layers of epidermis contain increased amount of melanin (silver and hematoxylin; × 45).

the brown pigmentation, while the "slaty" bluish-gray appearance of some areas was probably produced by viewing an increased amount of melanin through a greatly reduced number of superficial epidermal cells. In 7 of 13 biopsy specimens there was hemosiderin, varying in amounts from a trace to considerable quantities, in the connective tissue cells of the corium. It was usually concentrated in the cells about the acini of the sweat glands.

From these considerations it is apparent that if it is desired to use the presence of hemosiderin as a diagnostic criterion in hemochromatosis the gastric biopsy is a much more reliable aid than histological examination of the skin. Since the liver represents the depot of iron nearest the intestine, the liver must always show hemosiderosis, and for this reason a biopsy of this organ is the most certain way of confirming a suspected diagnosis of hemochromatosis. On the other hand, biopsy of the liver is not without an element of risk to the patient. For this reason the much simpler gastric biopsy should find a prominent place in the establishment of a diagnosis of hemochromatosis.

COMMENT

Studies with radioactive iron by Dubach, Callender, and Moore[20] established that the mechanism of excessive accumulation of iron in hemochromatosis is an abnormal increase in intestinal absorption of this metal. Since the actual cause of this increased absorption is still obscure, it is of interest to analyze the bearing which some of our data have on various etiological theories of hemochromatosis.

Several authors pointed out that the number of instances of familial occurrence of hemochromatosis is out of all proportion to the rarity of the disease and postulated a hereditary factor, as discussed by Rogers.[21] In our series, 2 of 23 patients have siblings with hemochromatosis and, thus, bear out this observation. In addition, we wish to call attention to the fact that a large majority of our male patients had moderate to marked sparsity of body and facial hair all their lives. This cannot be accounted for on the basis of hypogonadism, because loss of libido and testicular atrophy, when present in the same patient, were late manifestations of the disease in our series. One explanation is that the sparsity of hair is a constitutional characteristic of persons who are susceptible to hemochromatosis. An alternate explanation is that the sparsity of hair, and possibly also the pigmentation and atrophy of the skin, may be an early manifestation of the disease, which would indicate its presence at puberty in a large majority of male patients. Both explanations argue for an inborn predisposition to hemochromatosis. It is of interest that many male patients with portal cirrhosis of the liver also have sparsity of hair as a lifelong characteristic.

Certain grossly abnormal diets have been shown clinically and experimentally to lead to increased absorption and storage of iron, as well as to lesions in the liver. Gillman and Gillman [2] reported such a pathological picture in South African Negroes who live on a staple diet of corn and concluded that they were dealing with hemo-

20. Dubach, R.; Callender, S. T., and Moore, C. V.: Studies in Iron Transportation and Metabolism: VI. Absorption of Radioactive Iron in Patients with Fever and with Anemias of Varied Etiology, Blood **3**:526, 1948.

21. Rogers, W. F., Jr.: Familial Hemochromatosis, with Comments on Adrenal Function in Hemochromatosis, Am. J. M. Sc. **220**:530, 1950.

chromatosis. Experimentally, Kinney and co-authors [23] found that rats kept on certain diets grossly deficient in protein, minerals, and vitamins, with large supplements of ferric citrate, will absorb greatly increased amounts of iron and deposit it in the liver and other tissues. In addition, Hegsted and colleagues [5] demonstrated that gross diminution of phosphates in the diet will increase the absorption and storage of iron in rats. As a result of these experiments, the increased absorption and storage of iron observed clinically by Gillman and Gillman are now attributed to a disturbance of the iron-phosphorus ratio in the diet, while the fatty and fibrous changes in the liver can be ascribed to deficiency of dietary protein. A detailed nutritional survey of our patients with hemochromatosis failed to uncover any deficiencies in protein or important minerals and vitamins, except in a few cases and for such relatively short periods that disturbances of nutrition can be definitely excluded as an etiological factor in our series. The well-known adverse influence of alcoholism on nutrition was also ruled out in all but two of our patients.

Since in hemochromatosis the relation between the deposition of iron pigment in the liver, pancreas, and other organs and the functional and organic changes in these organs is not established, three possibilities must be considered: 1. Increased absorption and storage of iron is the primary cause of the disease, with all other manifestations secondary to this. 2. Changes in the liver, pancreas, and, possibly, other organs are primary and secondarily lead to increased absorption and storage of iron. 3. An unknown primary disturbance independently causes the abnormalities of iron metabolism and functional, as well as structural, changes in several organs. Recently accumulated evidence of several investigators favors the first possibility. Observations on transfusion siderosis, on the disorder resulting from chronic malnutrition in South African natives, and on excessive intestinal absorption of iron induced in rats by abnormal diet indicate that in all these conditions, similarly to hemochromatosis, iron is stored in excessive amounts as hemosiderin in the normal storage depots of the body. In addition, Granick [24] has shown the presence of normal ferritin in the duodenal mucosa and liver of a typical patient with hemochromatosis, thus supporting the thesis that in this disease the normal mechanism of iron absorption is concerned but is working to excess. Our liver biopsy specimens showed no anomalies in 3 of 14 patients, except for heavy deposits of hemosiderin. Two of these three patients had entirely normal responses to liver function tests, and the third patient showed slight impairment on two of seven such tests. We interpret this to indicate that hemosiderosis of the hepatic parenchyma, at least in a considerable proportion of patients with hemochromatosis, precedes all other hepatic changes. Interestingly, the patients who showed no hepatic fibrosis did not necessarily represent an earlier stage of hemochromatosis than those who did. Finally, repeated venesection for periods up to two years in three patients with hemochromatosis reported on by Davis and Arrowsmith [25] resulted in a return toward normal of the dextrose tolerance curve and the reactions to liver function tests. The authors also

22. Footnote deleted.

23. Kinney, T. D.; Hegsted, D. M., and Finch, C. A.: The Influence of Diet on Iron Absorption: I. The Pathology of Iron Excess, J. Exper. Med. **90**:137, 1949.

24. Granick, S., and Michaelis, L.: The Presence of Ferritin in the Duodenal Mucosa and Liver in Hemochromatosis, Proc. Soc. Exper. Biol. & Med. **66**:296, 1947.

25. Davis, W. D., Jr., and Arrowsmith, W. R.: The Effect of Repeated Bleeding in Hemochromatosis, J. Lab. & Clin. Med. **36**:814, 1950.

stated that serial liver biopsy specimens of these patients showed diminution in hemosiderin content and improvement in cirrhosis. Rapid regeneration of erythrocytes after venesection in these cases and in two other still unpublished cases of hemochromatosis indicates that, contrary to the older view, the iron is deposited in a utilizable form.

A serious objection to the view that excessive deposits of hemosiderin in some organs are responsible for functional and structural alterations in these organs lies in the fact that in several other organs fairly heavy deposits of this iron pigment produce no detectable changes in function or structure. An example of this is the gastric mucosa, in which our studies showed that, in spite of the presence of many hemosiderin granules in the chief cells, the secretion of pepsin remained normal. Furthermore, it is well known that even in organs which are recognized to suffer most in this disease, the extent of the functional and organic changes does not correspond to the amount of hemosiderin present. An instance of this is the fact that the severity of diabetes, when present, is independent of the degree of hemosiderosis in the pancreas. A possible explanation of such discrepancies may lie in the duration of hemosiderosis in a given organ or in unequal susceptibility of different organs to the noxious effects of the presence of hemosiderin. In any case, these objections are of sufficient importance to warrant continued consideration of the other two views regarding the causation of hemochromatosis until more evidence is obtained. Such evidence, amounting to proof in favor of the first view, could be produced if it were shown that repeated venesection, in addition to reversing the hemosiderosis, is capable of inducing arrest of the organic lesions and producing at least a partial correction of the functional manifestations of the disease over a period of many years in a sufficiently large number of patients with hemochromatosis.

Our cases of hemochromatosis in women bear out the present explanation of the rarity of this disease in females, namely, that hemosiderosis cannot develop because of the normal loss of iron through the menstrual blood.

Apart from hemosiderosis, the liver in our patients with hemochromatosis usually showed portal cirrhosis. However, the histological picture, with one exception, did not indicate active damage, since neither necrotic cells nor young fibrous tissue was present. Also, the histological changes usually were not those of nutritional cirrhosis. As a corollary to these histological indications of relative quiescence, the results of several liver function tests showed surprisingly little dysfunction in comparison with that found in other types of portal cirrhosis with a comparable degree of fibrosis. It is probable that the extreme chronicity of the disease accounts for these peculiarities of the cirrhotic process in hemochromatosis.

Changes in libido and the male sex organs, as well as the sparsity of body hair in males with hemochromatosis and with ordinary portal cirrhosis, have been said to be due to an excess of estrogens accumulated through failure of the diseased liver to destroy normal amounts of these hormones. However, in view of the otherwise relatively good function of the liver, this explanation is less likely to hold for hemochromatosis than for other forms of portal cirrhosis. On the other hand, sexual regression frequently occurs in malnutrition of long standing, as mentioned by Davies,[26] and it will be remembered that our patients presented a weight deficit averaging 8 kg. when they came under observation. Another possible explanation

26. Davies, J. N. P.: Sex Hormone Upset in Africans, Brit. M. J. **2**:676, 1949.

for the loss of libido and for the atrophy of the male sex organs lies in the changes, described by one of us,[10b] in the anterior lobe of the pituitary in a patient with this disease. Sparsity of body hair, as previously mentioned, must be kept separate from the sexual changes.

Turning to the pancreas, our study confirmed the more recent view that the diabetes associated with hemochromatosis usually does not present any difficulties in stabilization with diet and insulin. Such lack of difficulty may be due to the more effective modern treatment of the associated hepatic cirrhosis. At the moment, our results with the tests of the external secretion of the pancreas are difficult to interpret. It is true that in a considerable number of our cases in which these tests were done some impairment in the digestion of gelatin and hypersecretion of a dilute pancreatic juice in response to stimulation with secretin appeared to be present. However, before drawing any conclusions from these data, there is need for a study of various types of pancreatic and extrapancreatic disorders with these tests, so that a better idea may be obtained of the significance of deviations from the normal in terms of pancreatic disease and the possible range of changes in patients with extrapancreatic and, especially, hepatic diseases.

In regard to several other aspects of hemochromatosis, certain points are worthy of note. There was neither the hypotension nor the anemia mentioned by Sheldon.[1] In seven patients hypertension was present. Cardiac failure was noted for nine patients and was essentially due to ordinary heart disease. The series of electrocardiograms obtained showed no uniform changes. In two cases, in which at first a diagnosis of Addison's disease had been made, electrolyte levels did not support the view that the weakness was of adrenocortical origin.

In reviewing our factual knowledge of hemochromatosis, it is possible to outline part of the natural history of this disease. Its complete course covers many years. First, this is borne out by the statement of many patients that their symptoms were present for long periods, even up to 25 years or more in some instances. Second, it takes a long time to accumulate the total amount of iron found in the average person with hemochromatosis. On the basis of 20 mg. of iron ingested daily and fully absorbed, it would take more than seven years to reach 50 gm. And it is highly unlikely that intestinal absorption of iron is ever complete. Finally, the histological appearance of the liver is one of long-standing change. Therefore, hemochromatosis is a disease which starts at the latest in early adult life and has a long, slowly progressive course. There is no evidence of what precipitates the often sudden appearance of symptoms of diabetes, weakness, or hepatic cirrhosis. In the past, the presence of incapacitating symptoms led to the diagnosis, which was usually associated with a poor prognosis. However, when the disease is discovered incidentally, which at present happens much more frequently, the prognosis is much better. To complete this natural history, it will be necessary to diagnose and study earlier cases.

The recent discovery that the serum iron level is very high in hemochromatosis and that the iron-binding protein is saturated[27] led Granick[28] to suggest these

27. Rath, C. E., and Finch, C. A.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XXXVIII. Serum Iron Transport, J. Clin. Invest. **28**:79, 1949.

28. Granick, S.: Iron Metabolism and Hemochromatosis, Bull. New York Acad. Med. **25**:403, 1949.

procedures as screening tests. In a disease with an incidence of 1 case per 6,000 hospital admissions,[11] we feel that only clinical awareness, backed by the simplest laboratory methods, is of any practical use. Of the clinical features which should arouse suspicion, the most important are pigmentation of the skin, especially as seen on the forearms, atrophy of the skin, sparsity of body hair, and unaccounted-for hepatomegaly. In attempting confirmation of a clinical suspicion of hemochromatosis, the most important criterion is the presence of hemosiderin. For this reason a biopsy of the liver or of the gastric mucosa is of the greatest diagnostic value, although a high iron content of the serum, which was found in two-thirds of our cases, is also useful.

SUMMARY AND CONCLUSIONS

A study of 23 cases of hemochromatosis was made. In 15 of the patients a uniform predetermined plan of study was used. Data relating to etiology, to nutrition, to iron metabolism, and to a number of clinical and pathological features of this disease were obtained.

A constitutional factor in the etiology of hemochromatosis is strongly suggested by the incidence of this disease in siblings and by the lifelong sparsity of body hair in male patients, which antedates by many years evidence of sexual regression. Exogenous toxins were excluded as factors, and alcoholism was ruled out as the main factor in the etiology of hemochromatosis in our series.

Two-thirds of the patients had serum iron levels exceeding the upper limits of normal. Serum iron determinations repeated after an average interval of 15 months gave markedly higher figures.

Malnutrition in general and protein, as well as vitamin B complex, deficiency in particular can no longer be considered as possible etiological factors in hemochromatosis.

Excessive intestinal absorption of iron in hemochromatosis is not induced by alterations in the iron-phosphate ratio in the diet.

Recent investigations favor the hypothesis that excessive deposits of hemosiderin in normal storage depots of the body, secondary to excessive intestinal absorption of iron, are responsible for the characteristic disturbances of function and of structure in hemochromatosis. However, the possibilities that changes in the liver and in the pancreas may be responsible for the hemosiderosis, or that all three may have a common cause, are still not ruled out.

Markedly reduced menstrual loss of iron occurred in our three female patients, which agrees with the current explanation of the rarity of hemochromatosis in females.

Cirrhosis of the liver in hemochromatosis, as judged by clinical features, results of liver function tests, and the histological picture, is relatively benign as compared with other types of cirrhosis with a comparable degree of fibrosis.

Pancreatic function tests in a considerable proportion of cases showed impairment in digestion of gelatin and hypersecretion of a dilute pancreatic juice in response to stimulation with secretin. The significance of these findings is at present uncertain.

Electrolyte studies of two patients and blood pressure measurements in our series do not support the view that pigmentation and weakness in hemochromatosis are due to adrenocortical deficiency.

The "slaty" pigmentation so typical of hemochromatosis is due not to deposition of hemosiderin in the skin but to increased amounts of melanin in the basal layers seen through a greatly reduced number of superficial epidermal cells.

Hemochromatosis is a disease which starts in early life (probably before puberty) and runs a slow, progressive course. The prognosis of this disease is much better at present than when it was recognized only in its advanced stages.

Early diagnosis of hemochromatosis depends on the alertness of the physician for pigmentation of the skin (especially on the forearms), sparsity of body hair, unaccounted-for hepatomegaly, and unexplained weakness. A suspicion of hemochromatosis is best confirmed by biopsy of the liver or of the gastric mucosa.

Dr. I. J. Wood, Head of the Clinical Research Unit of the Walter and Eliza Hall Institute, gave frequent advice on our problem. Members of the Honorary Medical Staff of the Royal Melbourne Hospital permitted use of patients under their care. Officers of the Repatriation Commission made records available in several cases. Dr. Downie, Dr. King, Dr. Hayden, Dr. Leembruggen, and Dr. Robinson gave permission for use of their patients and assisted in other ways. Estimations of serum iron were done by Miss Beryl Splatt, of the Department of Biochemistry at the Royal Melbourne Hospital.

APPENDIX—BIOCHEMICAL METHODS

The following biochemical tests and determinations were used in this study:

Alkaline phosphatase, according to King and Armstrong.[29]

Amino acid nitrogen, by the method of Kravel.[30]

Quantitative bilirubin estimation, by the van den Bergh method.

Sulfobromophthalein test (dose, 5 mg. per kilogram of body weight; serum taken at 45 minutes; reading made in optical comparator).

Cephalin-cholesterol flocculation, according to Hanger.[31]

Gamma globulin, after Kunkel.[32]

Gastric fractional test meal after administration of 0.3 mg. of histamine; stomach emptied before injection and three times at half-hourly intervals after injection.

Hippuric acid test (as described by Quick): A. Intravenous method.[33] B. Oral method.[34]

Prothrombin time, according to Quick, as modified by Kark and Lozner.[35]

Serum albumin and globulin, after Howe, as modified by Hawk.[36]

Serum iron, after Powell.[6]

Thymol turbidity and flocculation, by the method of Maclagan as modified by Shank and Hoagland.[37]

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EFFECT OF VASOPRESSIN (PITRESSIN®)-INDUCED WATER RETENTION ON SODIUM EXCRETION

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THE EXCRETION of water is influenced by many factors. One of the most important factors is the antidiuretic hormone of the posterior lobe of the pituitary gland (ADH). An increase in the osmotic activity of the blood increases the secretion of antidiuretic hormone and results in a concentrated urine.[1] Drugs and reflex stimuli also release the antidiuretic hormone.[2] A decreasing osmotic activity of the blood inhibits the release of the antidiuretic hormone, and a water diuresis follows.

Small intravenous doses of vasopressin injection (pitressin®) in man produce the same effect on the excretion of water and salt as does endogenously produced vasopressin. Both act by increasing the tubular absorption of water without altering glomerular filtration or renal blood flow; neither have demonstrated in short-term experiments a striking effect on excretion of sodium chloride.[3] In water-loaded subjects administration of vasopressin may cause a slight decrease in the excretion of sodium.[4] The amount of sodium chloride being excreted does affect the degree of water antidiuresis.[5] By giving vasopressin intravenously every hour, the effect of a substance acting similarly to antidiuretic hormone on water and electrolyte excretion for a 24-hour period can be observed.

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5. Murphy and Stead.[3b] Rosenbaum, J. D.; Nelson, W. P., III, and Strauss, M. D.: Dependence of Water Diuresis upon Electrolyte Excretion, J. Clin. Invest. **29**:841, 1950.

The purpose of this study was to determine (1) the pattern of water excretion over a 24-hour period in a normal subject given (*a*) hypertonic, (*b*) isotonic, or (*c*) hypotonic sodium chloride solution; (2) the effect of repeated injections of vasopressin on the patterns of the water excretion; (3) the effect of periodic injections of vasopressin on the pattern of sodium, chloride, and potassium excretion.

CHEMICAL METHODS AND SUBJECTS

Sodium and potassium levels in serum and urine were measured in duplicate on a flame photometer [6]; serum and urinary chloride was measured by the silver iodate method.[7] Healthy medical students and house officers were used.[8]

HYPERTONIC SODIUM CHLORIDE SOLUTION

Methods.—For four days before the experiment, the subjects ate a 2,200-calory diet, containing 9 gm. of sodium chloride (155 mEq. of sodium). After four days the sodium excreted in the urine tended to be constant at about 100 mEq. daily. Presumably, the remainder of the sodium was excreted in the sweat and stool.

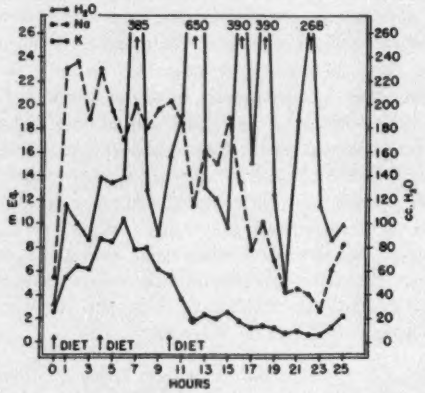

Fig. 1.—Graph showing results of study on one subject previously receiving 9 gm. of sodium chloride daily. At 8 a. m., 0 hour, subject was given 500 cc. of 5% sodium chloride solution (155 mEq. of sodium) intravenously, water ad libitum, and 9 gm. (155 mEq. of sodium) with meals. In this and subsequent figures, data for sodium, potassium, and water at 0 and 25 hours are mean figures for 24 hours preceding and following the experiment.

Hypertonic (5%) Sodium Chloride Solution Without Vasopressin Injection (Fig. 1).—Observations were made on three subjects. On the day of the experiment at 0 hour, 500 cc. of 5% sodium chloride solution (431 mEq.) was given intravenously in one hour. Urines were collected every hour. These subjects were allowed water ad libitum and a diet containing 155 mEq. of sodium chloride, divided into three equal parts, as indicated in the graph.

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7. Van Slyke, D. D.: Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

8. The vasopressin injection (pitressin®) used was manufactured by Parke, Davis & Company, Detroit 32.

Results: After the administration of 5% sodium chloride solution, the urine was concentrated for 5 to 10 hours, and the volume of urine was increased above the control level. During this period there was extreme thirst, and subjects drank large quantities of water. After 10 hours the urine became less concentrated and increased in volume. Thereafter, at irregular intervals relatively dilute and concentrated urines were produced, and in 24 hours there was no water retention, as shown by a return to control weight.

In the first 5 to 10 hours sodium concentration in urine was high (240 to 290 mEq. per liter). A high rate of sodium excretion was present within one hour. This gradually fell, and sodium excretion was normal at the end of 24 hours. Sixty to 90% of the sodium given was excreted in the urine. Loss by sweat and stool was not measured. High rates of sodium excretion were present with low and high rates of water excretion. Low rates of sodium excretion were present with high and low rates of water excretion. There seemed to be no correlation of sodium excretion with water excretion.

Sodium and chloride excretion paralleled each other well. After the administration of the hypertonic sodium chloride solution, there was a brisk potassium excretion for 10 hours.

Comment: The concentrated urine produced after the intravenous administration of 5% sodium chloride solution was apparently due to intense stimulation of osmoceptors, with secretion of large amounts of posterior-pituitary antidiuretic hormone. In spite of the effect of the antidiuretic hormone, the rate of water excretion was somewhat above the level before the injection of the 5% sodium chloride solution. This agrees with other observations that an osmotic diuresis caused by administration of the hypertonic salt solution cannot be inhibited by antidiuretic hormone.[3b] The irregularity in urine flow after the first eight hours indicates that sustained stimuli from the osmoceptors ceased, and the changes in urine flow were presumably due to varying reflex stimuli from emotions, exercise, and visceral activity, which have been shown to modify water excretion through the action of the posterior lobe of the pituitary.[2]

Maximum rates of sodium excretion were achieved in one to two hours. This indicates that the body is sensitive to excess sodium given in hypertonic solution and sets in motion at once the mechanism to increase the excretion of sodium.

Hypertonic (5%) Sodium Chloride Solution with Vasopressin Injection (Fig. 2).—Results: Observations were made on two subjects. These were not the same subjects who had received hypertonic salt solution alone. These subjects received vasopressin injection intravenously, 0.001 pressor unit per kilogram of body weight every hour for 24 hours.

After the administration of hypertonic saline solution and vasopressin injection, the rate and amount of water excretion were increased for eight hours; this was followed in the second eight hours by oliguria. In the last eight hours the rate and amount of water excretion were variable. The total water intake was not excreted in 24 hours; there was a weight gain of 2 kg., which was promptly lost the day after the experiment.

The concentration of sodium in the urine in the first eight hours was very high (190 to 250 mEq. per liter); in the second period the sodium concentration was less but still high. A high rate of sodium excretion was present within one hour.

This gradually fell and was not excessive at the end of 24 hours. Fifty per cent of the sodium given was excreted in 24 hours.

High rates of sodium excretion were present with relatively low rates of water excretion. Low rates of sodium excretion were present with high and low rates of water excretion, though after the fifth hour water excretion was always well below the average rate noted without vasopressin injection. While water excretion was greatly reduced, the pattern of sodium excretion was not modified. The difference in sodium excretion between the control and the vasopressin experiments is not significant because of the considerable variation in the rate of sodium excretion with a standard diet. Again after administration of hypertonic sodium chloride solution, there was a brisk potassium diuresis.

Comment.—Comparison of the hypertonic saline experiments with and without vasopressin injection reveals some similarities and some differences. The water excretion in the first eight hours was the same. Apparently the addition of vaso-

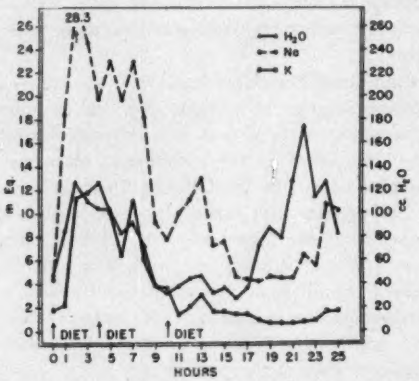

Fig. 2.—Graph showing results of study on one subject previously receiving 9 gm. of sodium chloride daily. At 8 a. m., 0 hour, subject was given 500 cc. of 5% sodium chloride solution (155 mEq. of sodium) intravenously, water ad libitum, and 9 gm. (155 mEq. of sodium) with meals. He received 0.001 pressor unit of vasopressin injection per kilogram of body weight intravenously every hour for 24 hours.

pressin to the endogenously produced antidiuretic hormone had little effect. However, in the second eight hours, water excretion was altered and oliguria was present. After the patient became hydrated, the normal periodic inhibition of release of antidiuretic hormone was masked by vasopressin. The weight gain of 2 kg. showed a striking impact on the water metabolism.

ISOTONIC SODIUM CHLORIDE SOLUTION

Methods.—Four days before the experiment, subjects ate a 2,500-calory diet containing 8 gm. (138 mEq. of sodium) of sodium chloride. After four days the sodium excreted in their urine tended to be constant at about 90 mEq. daily. On the day of the experiment, 2,780 cc. of isotonic (0.9%) sodium chloride solution (431 mEq. of sodium) was given intravenously in one hour. Urines were collected every hour. Water was allowed ad libitum. A diet containing 138 mEq of sodium chloride, divided into three equal parts as indicated, was given.

Isotonic Sodium Chloride Solution Without Vasopressin Injection (Fig. 3).—Results: Observations were made on two subjects. After administration of 0.9% sodium chloride solution, there was some delay in water excretion for four hours; this was followed by a substantially increased urine output and later by irregular variations in urine output.

Urine excreted in the first few hours had an intermediate sodium concentration (100 to 200 mEq. per liter). In the initial period, water and sodium excretion tended to parallel each other, but there were obvious exceptions when sodium excretion was relatively high and water excretion relatively low and when water excretion was relatively high and sodium excretion relatively low. In 24 hours 60 to 80% of the sodium had been excreted.

Comment: In the first hours the tendency to concentrated urine seemed related to the production of antidiuretic hormone. Because administration of 0.9% sodium

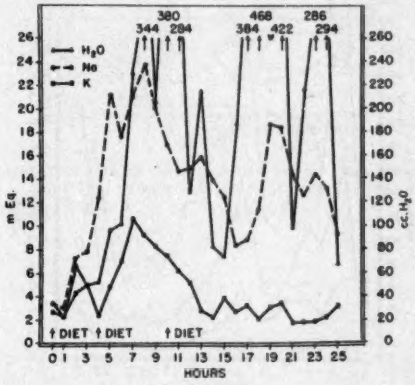

Fig. 3.—Graph showing results of study on one subject previously receiving 8 gm. of sodium chloride daily. At 8 a. m., 0 hour, subject was given 2,780 cc. of 0.9% sodium chloride (431 mEq.) intravenously, water ad libitum, and 8 gm. of sodium chloride (138 mEq. of sodium) with meals.

chloride solution did not cause maximal stimulation of the osmoceptors,[3b] the pattern of water excretion was less regular than after administration of 5% sodium chloride solution. After electrolyte loss and hydration removed a sustained osmotic stimulus, the familiar pattern of irregular diuresis and antidiuresis followed, this being related to the release of antidiuretic hormone by osmotic and reflex stimuli. Again excess sodium in the body was a strong stimulus to sodium excretion. Apparently 25 gm. of sodium chloride given as a hypertonic or as an isotonic solution is excreted in much the same way, except that the maximum rate of sodium excretion is achieved more quickly with hypertonic sodium chloride solution.

Isotonic Sodium Chloride Solution with Vasopressin Injection (Fig. 4).—Results: The two subjects studied were the same two who had received 0.9% saline solution previously. They were given intravenously 0.001 pressor unit of vasopressin per kilogram of body weight every hour for 24 hours.

Despite the vasopressin injection, the rate of water excretion increased (osmotic diuresis) in the initial periods. This was followed by relative oliguria until the morning hours, when water excretion increased. This increased excretion of water, in general, paralleled an increase in sodium excretion. The random irregularity in water excretion in the last two-thirds of the experiment was largely prevented by the vassopressin given. Total water excretion for 24 hours was less than the intake; subjects gained 2 kg. each.

The concentration of sodium in the urine tended to be between 150 and 200 mEq. per liter all day. Sixty-three to 90% of sodium intake was excreted. In general, the pattern of sodium excretion seemed not to be modified at all by the water retention due to the vassopressin injection.

Comment: Comparison of the isotonic saline experiments with and without vasopressin injection shows some similarities and some differences. In both there was an increased excretion of water which was not prevented by the vasopressin injec-

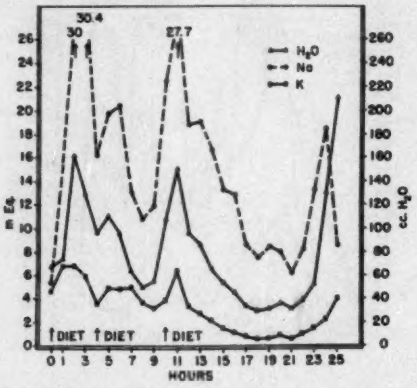

Fig. 4.—Graph showing results of study on one subject previously receiving 8 gm. of sodium chloride daily. At 8 a. m., 0 hour, subject was given 2,780 cc. of 0.9% sodium chloride solution (431 mEq. of sodium) intravenously, water ad libitum, and 8 gm. of sodium chloride (138 mEq. of sodium) with meals. He received 0.001 pressor unit of vasopressin injection per kilogram of body weight intravenously every hour for 24 hours.

tion. This appeared to result from the mechanisms responsible for increased electrolyte excretion and not from inhibition of the posterior lobe of the pituitary gland. In the last two-thirds of the experiment the water excretion was held to relatively low levels by the vasopressin. Despite the water retention, the pattern of sodium excretion was not modified.

In the last six hours the vassopressin inhibition was less effective. This has been observed repeatedly. It may be that there is always a minimal basal secretion of antidiuretic hormone by the posterior lobe of the pituitary gland and that under the strong stimulus of the 2 l. (2 kg.) of water retention this basal secretion comes to very low levels, and the exogenous vasopressin plus endogenous antidiuretic hormone is not enough to stimulate the renal tubules. On the other hand, the kidney may have inherent power to modify water excretion if the hormone regulators become disrupted.

HYPOTONIC SODIUM CHLORIDE SOLUTION

Methods.—Observations with and without vasopressin injection were made on 12 subjects. In eight experiments the observations without use of vasopressin were made first and those with vasopressin administration after an interval of three to five days. In four subjects observations with vasopressin injection were made first and those without use of vasopressin after an interval of three to four days. No differences were observed in the two groups.

Three days before the experiment these subjects ate a 2,500-calory diet containing 8 gm. (138 mEq. of sodium) of sodium chloride. On the morning of the experiment subjects were given 300 cc. of water. Thereafter, they drank 200 cc. of 0.2% sodium chloride solution every hour for 24 hours. This was an intake of 9.6 gm. of sodium chloride (165.5 mEq. of sodium).

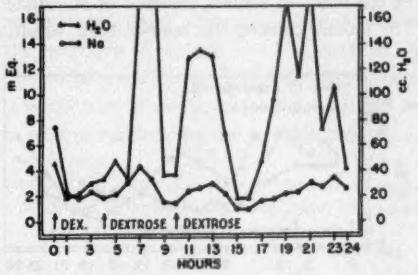

Fig. 5.—Graph showing results of study on one subject, previously receiving 8 gm. of sodium chloride daily. The subject received 200 cc. of 0.2% sodium chloride solution orally hourly, beginning at 8 a. m., 0 hour.

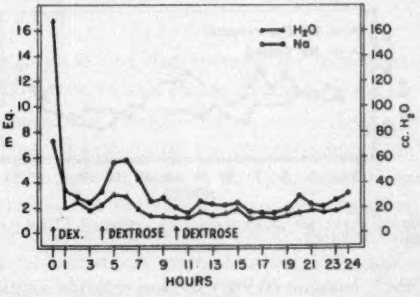

Fig. 6.—Graph showing results of study on one subject, previously receiving 8 gm. of sodium chloride daily. Hourly beginning at 8 a. m., 0 hour, subject received 200 cc. of 0.2% sodium chloride solution orally. Vasopressin injection, 0.001 pressor unit per kilogram of body weight, was administered intravenously every hour for 24 hours beginning at 0 hour.

Urines were collected every hour. Blood samples for electrolyte determinations were drawn at the beginning and at the end of the experiment. Fifty grams of dextrose were given in three divided doses, as indicated on the graph, to lessen metabolic acidosis.

Hypotonic Sodium Chloride Solution Without Vasopressin Injection (Fig. 5).—Results: During the oral administration of 200 cc. of 0.2% sodium chloride solution every hour, there was almost continually a large output of water, with occasional periods of relative oliguria. With 4,800 cc. of water intake, the output equaled the intake. There was no weight gain and no clinical evidence of edema. The sodium concentrations in the urine varied from 10 to 75 mEq. per liter.

There was a continuous excretion of sodium of 3 to 5 mEq. per hour. Despite a constant intake of sodium, there were at times irregular variations in excretion of sodium. In general, night excretion of sodium tended to be less than the day excretion. Chloride tended to be excreted at a faster rate than sodium, particularly in the first nine hours (Fig. 7).

Comment: The dilute solution reduced the osmotic pressure of the blood and inhibited the posterior lobe of the pituitary gland. A good water diuresis resulted which was interrupted irregularly by varying stimuli known to discharge the posterior pituitary.

Hourly intakes of 6.9 mEq. of sodium released or stimulated the sodium excretory mechanisms. The factors causing the hour-to-hour variation of sodium excre-

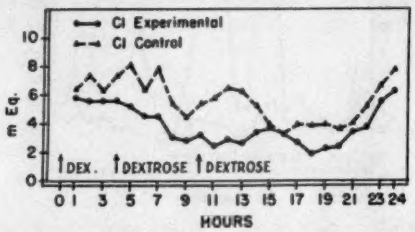

Fig. 7.—Graph showing curve for mean chloride excretion of 10 subjects receiving hypotonic sodium chloride solution.

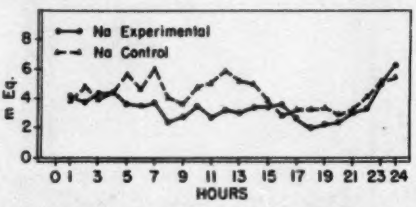

Fig. 8.—Graph showing curve for mean sodium excretion of 12 subjects receiving hypotonic sodium chloride solution.

tions are still not clear.[9] Isotonic (0.9%) sodium chloride solution is acid compared with body fluids. The higher rate of chloride than sodium excretion may be due to this.

Hypotonic Sodium Chloride Solution with Vasopressin Injection (Fig. 6).—Results: A continuous, sustained, uninterrupted antidiuresis was present. Clinically, this was reflected in extreme oliguria, despite a 4,800-cc. water intake and a weight gain of 2 to 4 kg. Edema of the face was often present at the end of 24 hours. In at least two subjects the concentration of sodium in the serum fell to 130 mEq. per liter. The concentration of the sodium excreted was 11 to 211 mEq.

9. Viar, W. N.; Oliver, B. B.; Eisenberg, S.; Lombardo, T. A.; Willis, K., and Harrison, T. R.: Effect of Posture and of Compression of the Neck on Excretion of Electrolytes and Glomerular Filtration: Further Studies, Circulation **3**:105, 1951. Adolph, E. F.: Regulation of Water Content of the Human Organism, J. Physiol. **55**:114, 1921.

per liter. From a study of composite curves for sodium excretion (Fig. 8) and from statistical analysis of eight-hour periods and of the 24-hour period (Table), vasopressin injection with its concomitant water retention made no significant difference in sodium excretion.

From the composite curves for chloride excretion (Fig. 7) and from the statistical analysis (Table) of data in the first and second eight-hour periods, it is evident that a minor but definite retention of chloride and potassium was caused either by the vasopressin itself or by the water retention.

Comment: The weight gain, the clinical evidence of edema, and the fall in the level of serum sodium indicated water retention. Despite this water retention and electrolyte dilution, the excretion of sodium was not modified. The retained water must have been distributed between extracellular and intracellular fluid. This overhydration of the cells would not be expected to cause sodium retention, as sodium does not play a major part in maintaining the osmotic pressure of the cells. It was

Twenty-Four-Hour Electrolyte and Water Excretion of Subjects Receiving Hypotonic Sodium Chloride Solution With and Without Vasopressin, Mean and Standard Deviation

No. of Experiments	Control, mEq.		Vasopressin, mEq.	
12	Na	95.42 ± 8	Na	79.16 ± 10
8	K	49.25 ± 3.74	K	35.37* ± 3.61
10	Cl	134.7 ± 8.88	Cl	91.4* ± 11.87
12	H_2O	3,812 ± 276	H_2O	982* ± 144

* Significant differences, $p < 0.05$.

somewhat surprising to us to find that lowering the concentration of extracellular sodium by dilution did not serve as a strong stimulus for sodium retention.

It is possible that under the conditions of these experiments the absolute amount of body sodium is more important than the concentration. Despite the dilution of body sodium, the body may be sensitive to the excess over the normal amount and set in motion a mechanism for the release of sodium. In short-term observations there was no evidence that vasopressin injection would cause a loss of sodium and, thus, mask an effect on sodium excretion of lowering the sodium concentration.[8b]

GENERAL COMMENT

If given salt and water patients with chronic congestive heart failure retain both.[10] At such a time sodium excretion is extremely low. Comparisons of this heart-failure group with subjects receiving vasopressin and hypotonic sodium chloride solution reveal similarities and differences. Both are retaining water; the experimental group is not retaining sodium; the patients with heart failure are. The data reported here do not support the hypothesis that water retention is important in the characteristic low renal excretion of sodium present in heart failure.

10. Merrill, A. J.: Mechanisms of Salt and Water Retention in Heart Failure, Am. J. Med. **6**:357, 1949. Futcher, P. H., and Schroeder, H. A.: Studies on Congestive Heart Failure: Impaired Renal Excretion of Sodium Chloride, Am. J. M. Sc. **204**: 52, 1942.

Antidiuretic substances have been found in the urine of edematous patients with (*a*) heart failure [11]; (*b*) cirrhosis of the liver [12]; (*c*) eclampsia,[13] and (*d*) nutritional edema.[14] It is to be expected that antidiuretic hormone from the posterior lobe of the pituitary gland will be found in the urine in most conditions in which salt retention occurs, as the retention of the electrolyte will serve to stimulate the osmoceptors and cause the release of antidiuretic hormone. This generalization does not exclude the possibility that in these conditions other antidiuretic substances may also be passed in the urine.

SUMMARY

The effect of vasopressin injection (pitressin®) on the excretion of water, sodium, chloride, and potassium was studied in normal subjects. They received hypertonic (5%) sodium chloride solution intravenously; isotonic (0.9%) sodium chloride solution intravenously, and hypotonic (0.2%) sodium chloride solution orally. Administration of either 5% or 0.9% saline solutions caused secretion of antidiuretic hormone and the production of concentrated urine. After the osmotic stimulus to the production of antidiuretic hormone was removed by electrolyte excretion or intake of water, the hourly rate of water excretion became variable. These data suggest that during ordinary activity the secretion of antidiuretic hormone is influenced more by reflex than by osmotic stimuli.

When variations in the effect of antidiuretic hormone on the renal tubules are reduced to a minimum by repeated injection of vasopressin, hourly rates of water excretion show much less variation. Under these conditions the amount of water excreted is influenced by the rate of sodium excretion.

Vasopressin injection had no demonstrable effect on the excretion of sodium, chloride, and potassium in the subjects receiving hypertonic and isotonic sodium chloride solutions.

In the subjects receiving 0.2% sodium chloride solution, use of vasopressin caused no demonstrable change in sodium excretion, in spite of marked water retention, and in two subjects, a considerable fall in the serum sodium concentration. Vasopressin injection did cause slight retention of chloride and potassium.

The data suggest that neither vasopressin nor endogenously produced antidiuretic hormone will produce the picture of sodium retention seen in congestive heart failure.

Mrs. J. H. Martin and therapeutic staff, May Dearing Nicholson and Gloria Kicklighter, cooperated in these experiments.

This work was accomplished with the technical assistance of Mrs. Ada Horowitz, Mr. Robert DeVore, Mr. Arthur Christokas, and Mr. Larry Oberc.

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13. Teel, H. M., and Reid, D. E.: Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, Endocrinology **24**:297, 1939.

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ADAPTATION TO ANOXIA IN CHRONIC PULMONARY EMPHYSEMA

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FOR MANY years there has been an intense interest in the adaptation of human beings to residence at high altitude. Numerous studies have been made of permanent residents of a mining district in Peru, where the altitude is 10,000 to 15,000 ft. (3,048 to 4,572 meters) above sea level. Residents of high altitude usually exhibit an increase in the hemoglobin content of the blood.[1] Moreover, with increasing altitude, and hence increasing anoxia, the elevation of the hemoglobin content of the blood becomes more marked. Anoxia also causes an increase in ventilation, with a resultant decline of the carbon dioxide tension in the alveoli and arterial blood.[2] The lowered carbon dioxide tension in the blood is compensated for by a decrease in bicarbonate, so that the blood pH remains normal.[3] There has been some disagreement on the effect of high altitude on cardiac output, but apparently the changes are small.[1a]

The physiologic changes which occur at high altitude serve as an adaptation to anoxia. The increase in the hemoglobin content of the blood enables the arterial blood to carry more oxygen to the tissues, and, as a consequence, the oxygen tension of the venous blood and presumably of the tissues is higher than if the blood had a normal hemoglobin content. The increased ventilation results in an increase in the

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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alveolar oxygen tension and permits a greater saturation of the arterial blood with oxygen.

Although the physiologic effects of anoxia due to high altitude have been carefully studied, much less attention has been devoted to the effects of chronic anoxia resulting from disease processes. Recently, a thorough study has been made of adaptation to anoxia in congenital heart disease.[4] There have been relatively few studies of the adaptation to anoxia in pulmonary emphysema. The studies which have been performed suggested that polycythemia and increase in hemoglobin content of the blood are less constant features in persons with pulmonary emphysema than in residents at high altitudes or in patients with cyanotic congenital heart disease.[5] Since pulmonary emphysema is the most frequent cause of chronic anoxia observed clinically, it was thought of importance to investigate further the problem of adaptation to anoxia in this disease, with particular emphasis on the hematologic aspects.

METHODS

Sixty-nine men with severe pulmonary emphysema were studied. The diagnosis was made on the basis of a history of dyspnea, together with the characteristic physical and roentgenographic findings. In addition, measurements were made of the residual air and total lung volume by the method of Cournand.[6] All patients had decidedly increased residual air, a relatively normal total lung volume, and a marked increase in the nitrogen content of the alveolar air at the end of 7 minutes of oxygen breathing. Measurements of the oxygen capacity, oxygen content, oxygen saturation of hemoglobin, carbon dioxide content, and pH of the arterial blood were made by methods utilized in a previous study.[7] Hematocrit determinations were obtained by centrifuging blood with heparin as an anticoagulant in 4-cc. hematocrit tubes at 3,000 rpm for 30 minutes. Determination of the hemoglobin content of the blood was performed on the Evelyn photoelectric colorimeter, which was standardized with blood of known hemoglobin content as determined by the oxygen capacity method. The serum iron was determined by the method of Barkan and Walker,[8] and the serum bilirubin, by the method of Malloy and Evelyn.[9] Reticulocytes were counted in a standard chamber using brilliant cresyl blue. Erythrocytes were counted in the usual manner, using standardized pipettes and chambers. Bone marrow was obtained by aspiration of the sternum.

RESULTS

The Hematologic Adaptation to Anoxia in Pulmonary Emphysema.—One of the purposes of the study was to determine whether the hemoglobin content of the

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blood was increased in a group of patients with severe emphysema. The oxygen capacity of the blood was used as a measure of its hemoglobin content. The mean value for the oxygen capacity of the blood in 69 patients with severe pulmonary emphysema was 19.86 vol. %, with a standard deviation of 2.4, a value which was similar to that of 19.58 vol. % obtained for 22 normal men. The mean oxygen saturation of the arterial blood in the patients with emphysema was 85.4 vol. %. Despite the normal mean oxygen capacity, there was a highly significant negative correlation between the oxygen capacity and the oxygen saturation of the arterial blood (Chart 1). The degree of correlation, however, was low ($r = -0.32$). There was no correlation between the carbon dioxide content of the arterial blood and the oxygen capacity ($r = 0.09$; Table 1).

It is interesting to compare the hematologic response to anoxia in patients having emphysema with the response in a group of permanent residents at high alti-

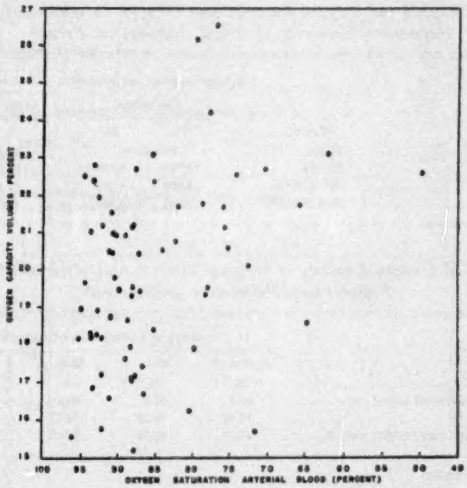

Chart 1.—Correlation between oxygen saturation and oxygen capacity of arterial blood of 69 patients with pulmonary emphysema ($r = -0.32$).

TABLE 1.—*Correlation Coefficients Among Oxygen Saturation, Carbon Dioxide Content, and Oxygen Capacity of Arterial Blood of Sixty-Nine Patients with Severe Pulmonary Emphysema*

r_{12}*	+ 0.0857
r_{13}	− 0.3178
r_{23}	− 0.6501
$r_{13.2}$	− 0.1678
$r_{12.3}$	− 0.3461

* Number 1 refers to oxygen capacity; number 2, to carbon dioxide content, and number 3, to percentage of oxygen saturation.

tude studied by Hurtado and Aste-Salazar.[2a] These authors found a progressive increase in the oxygen capacity of the blood with increasing altitudes (Table 2). With increase in altitude there was a decrease in the oxygen saturation of the arterial blood. If patients with pulmonary emphysema are divided into groups with

corresponding degrees of anoxia, the lack of hematologic adaptation to anoxia in emphysema is evident (Table 3).

The increase in erythrocyte count and hemoglobin content of the blood of residents at high altitude has been attributed to increased activity of the bone marrow. Increased numbers of reticulocytes are noted in the peripheral blood; the serum bilirubin is increased, and the bone marrow shows evidence of increased activity of the erythroid component.[10] The reticulocyte count of the peripheral blood in a group of patients with emphysema and anoxia showed no significant increase over the values in normal human beings (Table 4). The mean total serum bilirubin in nine of these patients was 0.4 mg. per 100 cc. The bone marrow was studied in 12 patients with emphysema and anoxia. The average arterial oxygen saturation in this group was 86%. The histologic appearance of the bone marrow was normal, and the erythroid cells composed 16.3% of the total, a value which is similar to that

TABLE 2.—*Values Obtained for Oxygen Capacity and Oxygen Saturation of Arterial Blood in Permanent Residents of High Altitudes in Peru*[2a]

No. of Subjects	Town	Elevation		Arterial Blood	
		Ft.	M.	Oxygen Saturation, %	Oxygen Capacity, Vol. %
38	Lima	Sea level		96.1	21.66
15	Oroya	12,240	3,730	87.6	24.97
18	Morococha	14,900	4,540	81.4	28.52
12	San Nicolás	15,940	4,860	80.7	29.04

TABLE 3.—*Relation of Oxygen Capacity to Oxygen Saturation of Arterial Blood in Sixty-Nine Patients with Pulmonary Emphysema**

	Oxygen Saturation of Arterial Blood, %				
	Above 90	85-90	80-85	75-80	Below 75
No. of patients	26	21	4	10	8
O_2 saturation of arterial blood, %	92.8	87.8	82.4	77.6	66.5
O_2 capacity, vol. %	19.41	19.15	19.77	21.84	20.83
CO_2 content of arterial blood, vol. %	47.77	56.65	59.77	63.98	67.90

* Mean values are given.

reported by Scott for normal subjects.[11] This is in contrast to the finding of 55.6% erythroid cells in the bone marrow of residents of high altitude studied by Merino and Reynafarje.[10b]

Although increase in the hemoglobin content of the blood was an inconstant feature in patients with anoxia and pulmonary emphysema, and evidence of increased erythropoiesis was lacking, changes in the size of the red cell were observed. The values for the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular hemoglobin concentration in a group of men with pulmonary emphysema and anoxia and a group of normal men are given in Table 4. A significant increase in the mean corpuscular volume and a significant decrease of the

10. (*a*) Hurtado and others.[1b] (*b*) Merino, C. F., and Reynafarje, C.: Bone Marrow Studies in the Polycythemia of High Altitudes, J. Lab. & Clin. Med. **34**:637-647 (May) 1949.

11. Scott, R. B.: Sternal Puncture in the Diagnosis of Diseases of the Blood-Forming Organs, Quart. J. Med. **8**:127-172 (April) 1939.

mean corpuscular hemoglobin concentration were noted in the patients with emphysema. The mean corpuscular hemoglobin was similar in the two groups. Price-Jones [12] observed an increase in the size of the erythrocytes in pulmonary emphysema and attributed this finding to retention of carbon dioxide. To determine the correlation among anoxia, carbon dioxide retention, and cell size, 25 patients with

TABLE 4.—*Comparison of Hematologic Values of Patients Who Have Pulmonary Emphysema and Anoxia with Normal Subjects**

	12 Normal Men	14 Patients with Pulmonary Emphysema
Oxygen saturation of arterial blood, %	.....	82.6 ± 7.5
Erythrocyte count, millions/cu. mm.	5.15 ± 0.15	5.04 ± 0.86
Hemoglobin content, gm./100 cc.	15.07 ± 0.75	15.34 ± 2.3
Cell volume, %	47.8 ± 1.8	51.7 ± 8.8
Mean corpuscular volume, cu. μ	92.8 ± 2.7	102.9† ± 6.8
Mean corpuscular hemoglobin, micromicrograms	29.3 ± 1.1	30.3 ± 1.7
Mean corpuscular hemoglobin concentration, %	31.5 ± 1.1	29.6† ± 1.5
Reticulocyte count, %	1.00 ± 0.99	1.06 ± 0.70

* Mean and standard deviations are given for each value.
† Statistically highly significant $P = < 0.01$.

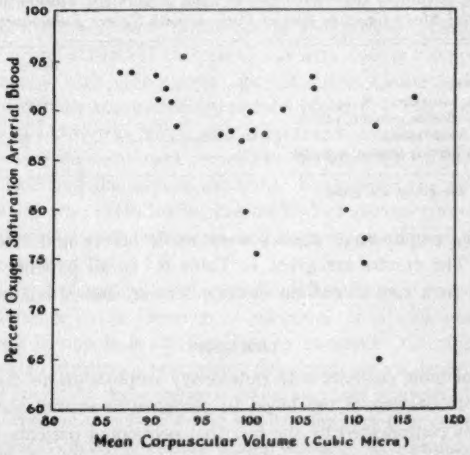

Chart 2.—Correlation between oxygen saturation of arterial blood and mean corpuscular volume of 25 patients with pulmonary emphysema and varying degrees of anoxia ($r = -0.56$).

emphysema and varying degrees of anoxia were studied. The results are given in Chart 2 and Table 5. The correlation between the oxygen saturation of the arterial

12. Price-Jones, C.: The Size of Red Blood Cells in Emphysema, J. Path. & Bact. **24**:326-332 (July) 1921.

blood and mean corpuscular volume was high ($r = -0.56$). There was no correlation between the carbon dioxide content and the mean corpuscular volume when the effect of oxygen saturation was removed by the technic of partial correlation.[13]

Chronic bronchial infection and repeated attacks of pneumonia are commonly associated with pulmonary emphysema. A decrease in the serum iron has been described in association with chronic infection and anemia.[14] The serum iron was determined in eight patients with severe pulmonary emphysema. The mean serum iron was 102 γ per 100 cc., with a standard deviation of ±26. The mean normal value for the laboratory was 122 γ per 100 cc., with a standard deviation of ±38.

The Effect of Anoxia on Ventilation in Pulmonary Emphysema.—In order to determine the role of anoxia in maintaining the level of ventilation in patients with

TABLE 5.—*Correlation Coefficients Among Mean Corpuscular Volume, Carbon Dioxide Content, and Oxygen Saturation of Arterial Blood of Twenty-Five Patients with Severe Pulmonary Emphysema*

r_{12}*	−0.5568
r_{13}	+0.4003
r_{23}	−0.4874
$r_{12.3}$	−0.4520
$r_{13.2}$	+0.1777

* Number 1 refers to mean corpuscular volume; number 2, to percentage of oxygen saturation, and number 3, to carbon dioxide content.

TABLE 6.—*Effect of Breathing One Hundred per Cent Oxygen for Twenty Minutes on Ventilation and Arterial Blood Gases in Eleven Patients with Severe Pulmonary Emphysema**

	Before	After
Ventilation, L/min.	11.7	8.8
Oxygen saturation, %	83.8	100
Carbon dioxide content, vol. %	58.1	62.1
pH of whole blood	7.39	7.31
Carbon dioxide tension, mm. Hg	50.3	63.1

*Mean values for the group are given.

severe pulmonary emphysema, studies were made before and after they breathed 100% oxygen. The results are given in Table 6. In all patients the breathing of oxygen resulted in a rise in carbon dioxide tension and a fall in the pH of the arterial blood.

COMMENT

The failure of most patients with pulmonary emphysema to display an increase in the hemoglobin content of the blood in response to anoxia was most puzzling. The problem was complicated by the fact that occasional patients with this disease have a marked increase in the hemoglobin content of the blood. Residents of high

13. Fisher, R. A.: Statistical Methods for Research Workers, ed. 9, Edinburgh, Oliver & Boyd, Ltd., 1944.

14. Cartwright, G. E.; Lauritsen, M. A.; Jones, P. J.; Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients, J. Clin. Invest. **25**:65-80 (Jan.) 1946.

altitudes, in contrast to patients with emphysema, regularly exhibit polycythemia in response to anoxia. The following reasons for this discrepancy may be considered:

1. Patients with emphysema are chronically ill and usually are malnourished.

2. The duration of the anoxia in these patients is less than in permanent residents of high altitudes.

3. Patients with pulmonary emphysema have an elevated carbon dioxide tension in the arterial blood, while residents of high altitudes have a reduced carbon dioxide tension.

4. Patients with pulmonary emphysema often have chronic bronchial infection and frequent episodes of pneumonia.

The poor nutrition and loss of weight in patients with emphysema appear inadequate to explain the lack of hematologic response to anoxia. Patients with cyanotic congenital heart disease are notoriously undernourished, and yet polycythemia is an almost constant feature.[4] The brief duration of the anoxia is also inadequate to explain the difference between patients with emphysema and residents of high altitudes. While it is true that the majority of the studies have been conducted on permanent residents of high altitudes, there is evidence that temporary residents also develop an elevation in the hemoglobin content of the blood in a brief period.[1b] Moreover, we have followed certain patients with emphysema and severe anoxia for many months without finding any increase in the hemoglobin content of the blood.

It is tempting to ascribe the difference in hematologic response to anoxia in emphysema on the one hand, and that in high altitude and in cyanotic congenital heart disease on the other, to a difference in the carbon dioxide tension of the arterial blood. Careful statistical analysis of our data does not support this hypothesis. As the patients with emphysema presented the findings of a compensated respiratory acidosis with approximately normal blood pH, the carbon dioxide content of the arterial blood was taken as a measure of the degree of carbon dioxide retention. There was no significant correlation between the carbon dioxide content of the arterial blood and the oxygen capacity. Even when the effect of anoxia on the oxygen capacity was excluded by the method of partial correlation,[13] no relationship between carbon dioxide content and oxygen capacity of the arterial blood could be demonstrated (Table 1).

The most likely explanation for the failure of hematologic response to anoxia in pulmonary emphysema is the presence of infection. It is well known that chronic infection depresses hemopoiesis and leads to an anemia.[14] Chronic infection of the bronchi and repeated attacks of pneumonia are characteristic features of pulmonary emphysema, and many of these patients have purulent sputum almost constantly. The presence of chronic infection would explain the fact that certain patients with pulmonary emphysema actually exhibit a mild anemia. The finding of only a slight decrease in the normal serum iron may be explained by the mild nature of the infection.

Occasional patients with emphysema exhibit marked polycythemia. Three of the 69 patients in the present series had an oxygen capacity greater than 24 vol. %. All three had severe anoxia and right heart failure. Other authors have noted the association of right heart failure and polycythemia in emphysema, and the South American authors have used the term Ayerza's disease for this combination of

findings.[15] The relation between the polycythemia and the right heart failure is not clear.

The finding of an increased mean corpuscular volume was a much more constant feature in patients with emphysema and anoxia than was the finding of an elevated hemoglobin content of the blood. Similar observations have been reported by Semenova.[16] The increase in the size of the erythrocyte appeared to be related to anoxia rather than to carbon dioxide retention. The finding of an increase in the volume of the erythrocyte in residents of high altitudes [15b] and in the newborn infant [17] also suggests a response to anoxia.

In residents of high altitudes the increase in ventilation serves as an adaptation to the lowered oxygen tension of the air. The increased ventilation leads to an increase in oxygen tension and to a decrease in carbon dioxide tension of both the alveolar air and the arterial blood. Experimental evidence indicates that this effect of anoxia on ventilation is mediated through chemoreceptors in the carotid and aortic bodies.[18] Emphysema interferes with normal alveolar ventilation, and, as a result, the alveolar carbon dioxide tension rises and the oxygen tension falls. In a previous study it was shown that patients with severe pulmonary emphysema and increase in arterial carbon dioxide tension were unable to lower the carbon dioxide tension significantly by voluntary hyperventilation.[7] This observation suggested that the resting ventilation was at the maximum level for carbon dioxide excretion.

The effect of breathing oxygen in patients with emphysema is of interest. A decrease in ventilation, together with an increase in carbon dioxide tension and a decrease in the pH of the arterial blood, was produced. Similar results have been reported by other workers [19] and demonstrate that anoxia in pulmonary emphysema stimulates ventilation. The altered sensitivity of the respiratory center in chronic emphysema to changes in carbon dioxide tension and pH of the blood is also demonstrated in that a decline of ventilation occurred in spite of a marked elevation of the carbon dioxide tension and a decline in the pH of the arterial blood.

Anoxia plays a minor role in the symptomatology of patients with pulmonary emphysema. The chief symptom is dyspnea. There is limitation of the maximum breathing capacity, and increased work is required to ventilate the lungs. Dyspnea appears to be related to the mechanical difficulty in moving air in and out of the lungs. As a result, the sensation of dyspnea occurs at a lower level of ventilation

15. (*a*) Taquini, A. C.; Fasciolo, J. C.; Suarez, J. R. E., and Chiodi, H.: Respiration and Circulation in Pulmonary Anoxemia, Arch. Int. Med. **82**:534-577 (Dec.) 1948. (*b*) Cournand, A.: The Fourth Walter Wile Hamburger Memorial Lecture, Institute of Medicine of Chicago: Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Diseases, Circulation **2**:641-657 (Nov.) 1950.

16. Semenova, K. N.: Hemopoiesis and Hemolysis in Certain Types of Respiratory Insufficiency, Klin. med. (No. 5) **5**:40-51, 1949.

17. Chuinard, E. G.; Osgood, E. E., and Ellis, D. M.: Hematologic Standards for Healthy Newborn Infants: Erythrocyte Count, Hemoglobin Content, Cell Volume, Color Index, Volume Index and Saturation Index, Am. J. Dis. Child. **62**:1188-1196 (Dec.) 1941.

18. Schmidt, C. F., and Comroe, J. H., Jr.: Functions of the Carotid and Aortic Bodies, Physiol. Rev. **20**:115-157 (Jan.) 1940.

19. (*a*) Taquini and others.[15a] (*b*) Baldwin, E. DeF.; Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency: III. A Study of 122 Cases of Chronic Pulmonary Emphysema, Medicine **28**:201-237 (May) 1949. (*c*) Comroe, J. H., Jr.; Bahnson, E. R., and Coates, E. O., Jr.: Mental Changes Occurring in Chronically Anoxemic Patients During Oxygen Therapy, J. A. M. A. **143**:1044-1048 (July 22) 1950.

than in a normal person. Early in the disease dyspnea occurs only on exertion, when the level of ventilation is markedly increased. With progress of the disease dyspnea occurs at rest with levels of ventilation only slightly abnormal.

The effect of anoxia on ventilation is desirable, in that anoxia increases oxygen tension and lowers carbon dioxide tension in the alveoli. Administration of oxygen to patients with emphysema and anoxia decreases ventilation and relieves at least partially the sensation of dyspnea. Unfortunately, the decline in ventilation increases the carbon dioxide tension in the blood and often results in uncompensated respiratory acidosis. The occurrence of coma after oxygen administration to patients with emphysema has been reported.[20] For this reason, oxygen should be administered with caution. Another disadvantage of oxygen therapy is that patients often become addicted to its use because of the relief of dyspnea which it affords. This can become a problem in hospitals because of the expense of this type of therapy if continued over a period of months. Oxygen therapy is best reserved for temporary episodes of severe anoxia precipitated by pulmonary infections and for the treatment of patients with complicating right heart failure. When the patient's condition improves, the oxygen therapy should be gradually discontinued. When oxygen is used, close observation should be made for the symptoms and signs of respiratory acidosis. The determination of the carbon dioxide content of the blood has proved useful in this regard. A sudden increase should serve as a warning of impending symptoms of respiratory acidosis.

Finally, the effect of anoxia on cardiac output in patients with emphysema should be mentioned. Prior to the advent of cardiac catheterization, accurate measurement of the cardiac output in patients with emphysema was difficult. With the advent of this technique, it was noted that patients with emphysema, cor pulmonale, and right heart failure could have either an increased or a normal cardiac output.[21] It was postulated that the increased cardiac output served as an adaptation to anoxia and decreased the ill effects of the anoxia in the disease by increasing the oxygen content of the venous blood. In a recent study of a group of patients with pulmonary emphysema without right heart failure, we [22] failed to find a correlation between the degree of anoxia and the arteriovenous oxygen difference. Thus, there was no evidence that an increase in cardiac output occurred as a response to anoxia in emphysema. This discrepancy has been recently explained by Cournand.[15b] He found a correlation between an increased blood volume and the cardiac output in patients with emphysema. Since hypervolemia characteristically accompanies heart failure, one could explain the increased cardiac output in these circumstances. Thus, it appears likely

20. Wilson and others.[7] Baldwin and others.[19b] Comroe and others.[19c] Barach, A. L.: The Effect of Low and High Oxygen Tensions on Mental Functioning, J. Aviation Med. **12**:30-38 (March) 1941.

21. Richards, D. W., Jr.: Cardiac Output by the Catheterization Technique, in Various Clinical Conditions, Federation Proc. **4**:215-220 (June) 1945. McMichael, J.: Circulatory Failure Studied by Means of Venous Catheterization, in Dock, W., and Snapper, I.: Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1947, Vol. 2, pp. 64-101. Ferrer, M. I.; Harvey, R. M.; Cathcart, R. T.; Webster, C. A.; Richards, D. W., Jr., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Digoxin in Chronic Cor Pulmonale, Circulation **1**:161-186 (Feb.) 1950.

22. Borden, C. W.; Wilson, R. H.; Ebert, R. V., and Wells, H. S.: Pulmonary Hypertension in Chronic Pulmonary Emphysema, Am. J. Med. **8**:701-709 (June) 1950.

that the increased cardiac output in pulmonary emphysema may be related to right heart failure and increase in blood volume rather than to anoxia per se.

SUMMARY

A study was made of the adaptation to anoxia in patients with pulmonary emphysema.

In contrast to residents of high altitudes, an increase in the hemoglobin content of the blood was seldom observed in patients with pulmonary emphysema and anoxia. Moreover, there was no evidence of increased activity of the bone marrow in 14 patients studied in this regard. The reason for this failure of hematologic adaptation to anoxia is not established, but it may be related to the presence of chronic bronchial infection. On the other hand, an increase in the mean corpuscular volume regularly occurs in these patients and is apparently the result of anoxia.

Breathing oxygen reduces the resting level of ventilation and leads to an increase in the carbon dioxide tension and a reduction of the pH of the arterial blood in patients with pulmonary emphysema and anoxia. Anoxia serves as an important stimulus to ventilation in these patients, and removal of this stimulus by means of oxygen therapy may result in coma associated with uncompensated respiratory acidosis.

Increase in cardiac output does not appear to be an important means of adaptation to anoxia in pulmonary emphysema.

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CLINICAL VARIETIES OF CHRONIC MYOCARDIAL INSUFFICIENCY

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CHRONIC myocardial insufficiency, already clinically of great importance, is becoming increasingly so with the current increase of old persons in our population. By chronic myocardial insufficiency I mean that form of heart disease in which myocardial insufficiency with or without myocarditis has developed in the absence of lesions of heart valves or pericardium. Another term for the condition is chronic nonvalvular heart disease.

The form or type of heart disease here discussed always has been of much importance because, beginning at about the age of 40, it steadily increases in frequency until in the later years of life it accounts for the great majority of patients consulting physicians or coming into hospitals because of symptoms and signs of heart disease. Furthermore, as people live longer, as now increasingly they do, there will be more and more patients with this form of heart disease. Only a few of these patients are young persons or children.

The pathologic feature of this form of heart disease of greatest interest to the clinician is the fact that, except for hypertrophy, in most cases so little departure from normal is found. In very few of these hearts is there extensive fibrosis. Notwithstanding the paucity of cardiac lesions, these hearts during life have failed to function normally, and for the majority of the patients cardiac decompensation is the chief cause of death. Usually after thorough study by the pathologist, no really satisfactory explanation of the why of this clinical development, and especially of its inception, can be given. Similarly, recent investigation of the chemical changes present in the myocardium of decompensated hearts has yielded no really satisfactory knowledge of the cause and particularly of what has started the myocardial insufficiency.

The clinician, however, is on more certain grounds in his understanding of chronic myocardial insufficiency than are the pathologist and the chemist. He can recognize certain types or groups of this variety of heart disease and can prophesy with considerable accuracy what will and what will not be found on postmortem examination. He can say, for example, that the valves will be found to be essentially normal in structure, that the pericardium at most will show only so-called milk patches, that the heart muscle, as a rule, will be of normal color and texture, and that the coronary arteries will show no more than a minor degree of arteriosclerosis, except in those hearts in which chronic myocardial insufficiency has been a sequel to infarction correctly diagnosed during life.

Clinically, patients with chronic myocardial insufficiency can be subdivided into several quite distinctive groups, as follows: (1) those with hypertension, (2) those without hypertension, (3) those with chronic bronchitis and pulmonary emphysema, (4) those with diffuse chronic myocarditis, (5) those whose chronic myocardial insufficiency is sequential to myocardial infarction, (6) those in whom it is a result of vitamin deficiency, (7) those in whom it results from amyloidosis of the myocardium, (8) those with chronic myocardial insufficiency in glycogenosis (von Gierke's disease), cardiomegalia glycogenica, (9) those in whom it is a result of fatty infiltration of the heart, (10) those in whom it results from neoplasm of the heart, (11) those in whom it follows parasitic infection of the heart, (12) those in whom it results from cardiac atrophy, (13) those whose disease is of endocrinopathic origin, (14) those whose disease is in hemochromatosis, and (15) those in whom it is associated with idiopathic congenital hypertrophy of the heart.

More patients fall into Group 1 than into the others. In Group 1 hypertension precedes the appearance of signs and symptoms of cardiac insufficiency usually by quite a long period, but sometimes by only a short time, a few weeks rather than months or years. Prior to the appearance of evidences of cardiac insufficiency usually enlargement of the heart is present and can be detected clinically, but neither statement is always true. Cardiac size may increase only slowly, or infrequently enlargement may be rapid in its development. These statements refer to a continuing enlargement indicative of hypertrophy preponderating over dilatation, although both will be present to some degree in almost all these hearts.

Increase in heart size of short duration suggests that dilatation is the main cause of the cardiac enlargement and insufficiency, particularly if later a decrease in heart size can be demonstrated. In an occasional patient dilatation is almost the sole cause of increase in heart size, and if such patients die, the heart post mortem may be of almost normal size and weight. Such patients have been reported as dying of heart disease with hearts that appeared normal on pathological examination, since the dilatation demonstrable during life disappeared during the process of rigor mortis. Unfortunately, the clinician either by physical examination or by roentgenologic study is unable in a given patient to determine accurately whether dilatation or hypertrophy preponderates, though sometimes this can be inferred from the patient's history of the character and rate of appearance of symptoms of cardiac insufficiency and the development of abnormal rhythms, especially tachycardia with or without fibrillation. Usually in patients with enlarged hearts both hypertrophy and dilatation are present, and probably there have been periods in which dilatation has dominated over hypertrophy and other periods in which the reverse has been true.

The degree of increase in blood pressure cannot be synchronized closely with the increase in heart size. This is especially true of increase in systolic pressure, less so for diastolic pressure; but in some patients long-continued high systolic and diastolic pressure will fail to cause much change in heart size, while in others a short period of such hypertension will be followed by easily demonstrable cardiac enlargement. In the same way, there may be no close relationship between heart size and symptoms and signs of cardiac insufficiency. Very large hearts may be found to be functioning well, while much smaller ones are functioning inefficiently.

Another inconstant feature in the group having chronic myocarditis with hypertension is the speed with which evidences of cardiac insufficiency develop. In

some patients there is a gradual, long-drawn-out period between very moderate and marked cardiac insufficiency, while other patients pass quickly, or even abruptly, from no signs and symptoms to serious ones.

The striking variations described in the preceding pages between degrees and time relationships of hypertension and cardiac insufficiency necessarily create doubt regarding the exact causal relationship of the two processes. It may be that the hypertension is only an added burden on a heart destined to run its course of insufficiency, a condition which has some other primal cause than the hypertension. This idea has additional support in the fact that we see the same sequence of myocardial insufficiency in numerous patients who never have had hypertension. For these reasons, I prefer for the condition of the group of patients just discussed not to use the term hypertensive heart disease, but rather the term chronic myocardial insufficiency with hypertension.

Group 2 of patients with chronic myocardial insufficiency is made up of those with all the features just described for the group with hypertension, but in whom at no time has there been an antecedent hypertension. These patients will run their entire clinical course with blood pressure within normal limits except for possibly a slight elevation during periods of chronic passive congestion, an elevation which disappears when chronic passive congestion is relieved by treatment. This group of patients is much larger than is generally recognized. I have followed numerous ones through their course, and I have the impression that with increase in persons in older age groups these patients are increasing in frequency. I am certain that they are not as unusual as is implied by various published studies of them. Possibly they comprise one-quarter of patients with chronic myocardial insufficiency.

In Group 3 of patients with chronic myocardial insufficiency and slight or no hypertension are many with a distinctive clinical picture, patients in whom the heart disease is a sequence of chronic pulmonary disease with, at first, recurring bronchitis accompanied with cough and dyspnea and with, eventually, almost continuous bronchitis, persistent cough, dyspnea, and, often, cyanosis. In the later period of this sequence symptoms and signs of cardiac insufficiency develop, usually responding at first to treatment, later relapsing, and, eventually, running a course like that in the first and the second groups already described. The condition of these patients may be called chronic myocardial insufficiency with chronic emphysema and bronchitis with or without hypertension, more usually without than with.

In these patients there is, as a rule, a quite typical conformation of the thorax and abdomen. They have a barrel-shaped chest, with the anteroposterior diameter increased in ratio to lateral measurements. The lower ribs flare out, and the distance between ribs, particularly the lower ribs, is increased. The abdomen tends to protuberance. With respiration the ribs move but little, and the diaphragm, low in position and with a decrease in its normal domed shape, has a reduced respiratory movement. Respiration is abdominal rather than thoracic. Often these patients are overweight.

Cardiac insufficiency, with a few exceptions, is a sequence of a gradual development of the conformation of thorax and abdomen which has been described in

the preceding paragraph. A long time usually is required for this development. Emphysema of the lungs in these patients, as a rule, is diffuse, with moderate increase in size of the air sacs but without the formation of large bullae except for, sometimes, a few of them along the anterior margins of the lobes of the lung. The chief functional disturbance in the lungs is a lessened elasticity which decreases expiratory activity.

With this apparent mechanism of cardiac insufficiency one would expect the heart to develop the form and function of cor pulmonale, with preponderating and continuing right-sided failure. However, it seems that in these patients far oftener there is left-sided or simultaneous right- and left-sided heart failure after an earlier stage of cor pulmonale and right-sided failure.

There are differences of opinion with regard to the part played by pulmonary emphysema in the mechanism of this clinical syndrome which eventuates in chronic myocardial insufficiency. One group considers that emphysema of the lungs is an important factor in the causation of the changed thoracic and abdominal contour and the decreased respiratory function. Another group believes that the emphysema results from changes, otherwise caused, in the shape and function of the thorax. A third group thinks both types of change develop in an interrelationship in which neither can be said to be of primary significance in causation of the progressive deterioration that takes place in pulmonary and cardiac function. In most patients pulmonary disturbances are causative of the chronic myocardial insufficiency and antedate it. In some the two processes are not closely related. The chronic myocardial insufficiency is of the type of Groups 1 and 2 which develops while the emphysema is appearing.

It is of interest that there is a clinical type of pulmonary emphysema found most frequently in patients beyond 65 years of age, in whom the changes in shape of the thorax just described do not occur and myocardial insufficiency does not develop. Many of these patients never display chronic pulmonary or cardiac insufficiency, although at autopsy the lungs will show extensive emphysema with many large bullae.

Patients of Group 4 are quite few. Their chief lesion is diffuse fibrosis of the myocardium, a chronic diffuse myocarditis. Sometimes it is a sequence of so-called acute isolated, or Fiedler's, myocarditis. Often it is not diagnosed during life. Hypertension usually is not present. Progression of signs and symptoms of cardiac insufficiency is apt to be rapid, and various arrhythmias are frequent and tend to persist. The presence of the features just mentioned sometimes leads to a correct clinical diagnosis for these patients' condition.

A fifth group of patients, not very numerous in ratio to the great frequency of coronary occlusion, in whom chronic myocardial insufficiency occurs is composed of those who have survived for a considerable time the development of a large infarction of the myocardium caused by coronary disease. Such infarction in its healing results in localized fibrosis extensive enough to decrease cardiac function. Often there results an aneurysmal dilatation of the ventricle at the site of the infarct. Hypertension may or may not be present. Rarely, chronic myocardial insufficiency follows coronary disease without infarction of myocardium.

Vitamin deficiency is causative of chronic myocardial insufficiency in a sixth group of patients. From a deficiency in the diet of B-complex vitamins, especially

thiamine, a distinctive form of heart disease develops, so-called beriberi heart. Some investigators also think that vitamin E deficiency may be productive of myocardial insufficiency.

Amyloidosis, glycogenosis, fatty infiltration, and neoplasia involving the myocardium extensively are the cause of chronic myocardial insufficiency in a few patients, Groups 7, 8, 9, and 10. Group 11 are patients with parasitic infection of the myocardium. Trichinosis rarely causes a diffuse myocarditis of sufficient extent to produce chronic myocardial insufficiency. In South America Chaga's disease (American trypanosomiasis), caused by Trypanosoma cruzi, is increasing in frequency. Infection of the myocardium by this parasite often leads to myocardial insufficiency, either acute or chronic, with a marked tendency to progression and a poor prognosis. Infection with the organism, Trypanosoma rhodesiense, causative of African trypanosomiasis, sometimes among other more important disturbances, leads to myocardial insufficiency. Rarely, an intracardiac worm is causative of myocardial insufficiency in man, although Dirofilaria immitis causes it in dogs.

In old persons the heart often shows at postmortem examination atrophy of the muscle cells with increased pigmentation. However, usually these patients do not have the clinical symptoms and signs of chronic myocardial insufficiency. When they do, they make up Group 12 in our classification. Very rare is a patient with chronic myocardial insufficiency in whom autopsy reveals a dilated heart with thinned ventricular walls; the etiology of this is not known.

In Group 13 are patients who display the symptoms and signs of chronic myocardial insufficiency as part of an endocrinopathic complex. This is not infrequent in hyperthyroidism. It is particularly important to recognize it when the hyperthyroidism is masked. In a few patients myxedema is accompanied with myocardial insufficiency. Less frequently, hyperpituitarism is causative, as seen in acromegaly. Hyperadrenalism, too, may be a causative factor of chronic myocardial insufficiency indirectly by reason of its associated hypertension in that group of patients in whom the hypertension is persistent rather than paroxysmal. Hypoadrenalism does not cause myocardial insufficiency in the sense that the latter term is used clinically.

Group 14 is composed of the occasional patients with hemochromatosis involving the myocardium to such a degree that myocardial insufficiency results. In this group are to be placed patients who have what has been called, largely by French physicians, the endocrinohepaticocardiac syndrome with rapid development of cardiac failure with extensive anasarca; these patients show pigmentation of the skin, usually, but not always, hemochromatotic cirrhosis of the liver, and evidence of polyglandular insufficiency and infantilism. There is also the possibility of myocardial insufficiency from ovarian dysfunction.

Finally, there is Group 15, patients with chronic myocardial insufficiency from idiopathic or congenital cardiac hypertrophy. The conditions of some patients formerly grouped here now are classed as cardiomegalia glycogenica (Group 8) or as diffuse rhabdomyoma (Group 10). This leaves a rare patient who still may be considered as one with idiopathic or congenital cardiac hypertrophy. Except for their early age these patients resemble those of Group 2, patients with chronic myocardial insufficiency without hypertension.

The treatment of most patients with chronic myocardial insufficiency should be digitalis, diuretics, salt restriction and resins, along with such special therapy as is needed to control or stop accompanying arrhythmia. In addition to this, patients in Group 3 will need treatment of their accompanying bronchitis and pulmonary edema. Patients in Group 6, notably those with thiamine deficiency, should receive their lacking vitamin. When the myocardial insufficiency is of parasitic origin (Group 11) the causative parasitosis should be treated by any effective antiparasitic therapeutic agent. If myocardial insufficiency is caused by an endocrine disturbance, the endocrinopathy should be treated by appropriate medical and surgical measures.

SUMMARY

By chronic myocardial insufficiency is meant that form of heart disease in which there is an absence of lesions of heart valves or pericardium. It also has been called chronic nonvalvular heart disease. It is striking how few changes are found in the heart muscle of these patients beyond hypertrophy. Clinically there are 15 groups of patients with chronic myocardial insufficiency. These are described.

MYOCARDIAL INFARCTION WITH AND WITHOUT ACUTE CORONARY OCCLUSION

A Pathologic Study

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THE CONCEPT of inadequate coronary blood flow resulting from chronic atherosclerotic narrowing of the coronary arteries as a cause of myocardial infarction without acute occlusion has become rather generally recognized.[1] Among the first pathologic observations of acute myocardial infarction without the presence of an acute coronary occlusion were the studies of Büchner.[2] Blumgart, Schlesinger, and Zoll [3] have stressed the fact that coronary thrombosis or occlusion does not always produce myocardial infarction and, conversely, that acute myocardial infarction may occur in the absence of acute coronary occlusion. They have demonstrated this particularly by the technic of studying the coronary arteries after injection of radiopaque compounds. Experimentally, both the severity and the duration of the hypoxia of the myocardium occurring with coronary insufficiency would seem to determine whether the changes will be transient and reversible or be characterized by necrosis of the myocardium.[4]

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1. Master, A. M.; Gubner, R.; Dack, S., and Jaffe, H. L.: Differentiation of Acute Coronary Insufficiency with Myocardial Infarction from Coronary Occlusion, Arch. Int. Med. **67**:647-657 (March) 1941. Horn, H.; Field, L. E.; Dack, S., and Master, A. M.: Acute Coronary Insufficiency: Pathological and Physiological Aspects: Analysis of 25 Cases of Subendocardial Necrosis, Am. Heart J. **40**:63-80 (July) 1950. Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Studies on Relation of Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to Pathologic Findings, with Particular Reference to Significance of Collateral Circulation, ibid. **19**:1-91 (Jan.) 1940.

2. Büchner, F.: Die Rolle des Herzmuskels bei der Angina pectoris, Beitr. path. Anat. **89**:644-667, 1932.

3. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction: Role of Coronary Occlusion and Collateral Circulation, J. A. M. A. **116**:91-97 (Jan. 11) 1941.

4. Burchell, H. B.: Adjustments in the Coronary Circulation After Experimental Coronary Occlusion, with Particular Reference to Vascularization of Pericardial Adhesions, Arch. Int. Med. **65**:240-262 (Feb.) 1940. Blumgart, H. L.; Gilligan, D. R., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries: II. The Production of Myocardial Infarction, Am. Heart J. **22**:374-389 (Sept.) 1941.

The primary purpose of this study was to determine whether, in the absence of an acute coronary occlusion, hypertrophy of the heart had an influence in precipitating gross myocardial infarction. With this in mind, a consecutive series of hearts showing acute myocardial infarction without acute coronary occlusion was studied. In addition, in these cases the distribution and extent of the infarcts, as well as the complications, were compared with the frequency and nature of these factors in a control group of cases in which myocardial infarction had followed acute coronary occlusion.

MATERIAL AND METHOD

The total series, including controls, was made up of cases in which (1) death occurred in Rochester, Minn., (2) necropsy was performed by members of the Section on Pathologic Anatomy of the Mayo Clinic in the four-year period, Jan. 1, 1946, through Dec. 31, 1949, and (3) an acute myocardial infarct was observed. About three-fourths of the patients resided in Rochester or the surrounding rural community. Only those cases were included in which the infarcts histologically appeared to be less than four weeks old as based on the criteria of Mallory, White, and Salcedo-Salgar.[5] The infarct in each case measured at least 2 cm. in at least one diameter. The ventricles of the preserved hearts were visualized grossly in five serial planes transverse to the long axis of the heart. The coronary arteries were cross-sectioned at 3-mm. intervals along their entire course. Multiple histologic sections of the coronary arteries were studied to confirm or alter gross impressions concerning the presence or absence of acute occlusion. Coronary sclerosis was graded on the basis of the severest involvement in each vessel; the sclerosis was graded 1, 2, 3, or 4 when the cross-sectional diameter was narrowed 25, 50, 75, or 100%, respectively. Grades of 1+, 2+, and 3+ were used in a few instances in which sclerosis could not be more generally classified; these grades were given a value of 1.5, 2.5, and 3.5, respectively, in determining average degrees of sclerosis of the various portions of the coronary arterial tree.

The table of expected cardiac weight of Smith[6] was used in determining the degree of cardiac hypertrophy for each patient. In each case the body weight of the patient was obtained from the last recorded weight on the clinical record, or, when this was not available, the estimated body weight at necropsy was used. For each heart the difference between the actual weight and the expected normal weight was determined, and this difference was considered to represent the number of grams of hypertrophy. This figure was divided by the expected normal weight of the heart and multiplied by 100, giving the percentage above or below normal weight for that heart.

RESULTS

Incidence of Acute Coronary Occlusion as Compared with That of Coronary Insufficiency in Acute Myocardial Infarction (Table 1).—Among 3,057 necropsies performed by members of the Section on Pathologic Anatomy of the Mayo Clinic during the four-year period concerned, 143 cases of acute myocardial infarction fulfilled the criteria established for this study. In 94 of these 143 cases (66%) acute coronary occlusion was present. Single or multiple thrombosis occurred in 90 instances, in seven of which thrombosis was superimposed on hemorrhage into an atheroma. Occlusion by intimal hemorrhage alone occurred twice. Embolic occlusion from valvular vegetations was seen in two instances. In 49 cases (34%) no recent thrombosis or other form of acute occlusion in any of the coronary arteries was seen. In each instance the coronary insufficiency leading to acute myocardial

5. Mallory, G. K.; White, P. D., and Salcedo-Salgar, J.: The Speed of Healing of Myocardial Infarction: Study of the Pathologic Anatomy in 72 Cases, Am. Heart J. **18**:647-671 (Dec.) 1939.

6. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79-93 (Oct.) 1928.

infarction was related, from the morphologic viewpoint, to coronary sclerosis either alone or in association with old organized thrombi in the coronary arteries.

Sex and Age Incidence.—Of the 143 patients 93 were men (65%) and 50 were women (35%). Of the 94 patients with acute coronary occlusion, 65 were men and 29 were women, a ratio greater than 2 males to 1 female. In the group of 49 patients with acute coronary insufficiency the proportion of men to women was roughly equal—28 were men and 21 were women.

The average age at death of men with acute coronary occlusion was 64 years, and of those with acute coronary insufficiency, 56 years. The average age at death of women in both groups was 69 years. Otherwise, the findings in men and women were the same, and no further differentiation as to sex will be made in this presentation.

TABLE 1.—*Incidence of Acute Coronary Occlusion as Compared with That of Coronary Insufficiency in Acute Myocardial Infarction*

	Cases	Per Cent
A. Acute coronary occlusion	94	66
1. Acute thrombosis	90	63
(Multiple [2] acute thrombi)	(7)	(5)
2. Complete occlusion by intimal hemorrhage alone	2	1
3. Embolic occlusion (vegetative endocarditis)	2	1
B. "Acute coronary insufficiency"	49	34
Total	143	100

TABLE 2.—*Cardiac Hypertrophy in Acute Myocardial Infarction*

	In Cases of	
	"Acute Coronary Insufficiency"	Acute Coronary Occlusion
Average hypertrophy, % above normal	70	50
Hypertrophy more than 50% above normal, % of hearts	74	42

Seasonal Incidence.—In neither group was there any striking difference in frequency of death due to acute myocardial infarction in any one season as compared with another. There were 43 deaths during the winter months, December through February, 36 in the spring, 33 in the summer, and 31 in the fall.

Cardiac Hypertrophy (Table 2).—A wide range in the degree of cardiac hypertrophy was seen in both groups of patients, resulting in a marked overlapping of the range in weights of the two groups. However, the average hypertrophy in the patients with acute coronary insufficiency was 70% above normal, as compared with 50% for those with acute coronary occlusion. Approximately three-fourths (74%) of the patients with coronary insufficiency had hearts weighing more than 50% above the expected normal weight, while in less than half (42%) of the control group the cardiac hypertrophy was more than 50% above normal. Fifty-three per cent of the patients with acute coronary insufficiency had a history of hypertension, as compared with 30% of the patients with acute coronary occlusion. Previous cardiac decompensation had occurred in 39% of the group with coronary insufficiency, as compared with 19% of those with recent coronary occlusion. One

patient in the entire study had mitral stenosis. Calcific aortic stenosis was noted in three patients with, and in one patient without, acute coronary occlusion.

Coronary Sclerosis.—The average grade of sclerosis of the anterior descending coronary artery was 3.0 in both groups of cases. In the left circumflex and right coronary arteries the average grades of sclerosis were 2.4 and 2.6, respectively, in the cases in which there was coronary insufficiency and 2.7 and 2.7, respectively, in the cases in which there was acute coronary occlusion. Whereas coronary sclerosis of Grade 3 or more in the anterior descending artery was present in more than three-fourths of the cases in each group, sclerosis of similar severity was present in the other two major arteries in about half the cases in each group.

Location of Acute Myocardial Infarcts in Relation to Coronary Supply.—In almost all cases a predominant zone of infarction was evident, although occasionally focal necrosis existed, especially in cases of coronary insufficiency without occlusion. Anterior and anterolateral infarcts were somewhat commoner with nonocclusive coronary insufficiency than with acute coronary occlusion. Of 49 cases of myocardial infarction due to coronary insufficiency, in 37 (76%) the infarct was in an anterior or anterolateral location, while in only 11 (22%) the infarct was

TABLE 3.—*Incidence of Acute Myocardial Infarcts According to Type*

	"Acute Coronary Insufficiency"		Acute Coronary Occlusion	
Type of Infarct	Cases	% of 49 Cases	Cases	% of 94 Cases
Predominantly transmural	9	18	84	89
Predominantly subendocardial	40	82	10	11

posterior. In contrast, of the 94 cases in which there was acute coronary occlusion, in 54 (57%) the infarct was in an anterior or anterolateral location, while in 37 (39%) the infarct was posterior. In one case of the group with coronary insufficiency and in three of the group with coronary occlusion, the infarcts did not conform to the classic anterior, anterolateral, or posterior distribution. The greater frequency of occurrence of anterior and anterolateral infarcts in the coronary insufficiency group as compared with posterior infarcts may possibly be dependent upon the greater degree of narrowing of the anterior descending coronary artery as compared with the other two major coronary arteries.

Character and Distribution of Acute Myocardial Infarcts in the Cardiac Wall (Table 3).—Transmural infarcts of the left ventricle were seen mainly in the group with acute coronary occlusion. Eighty-nine per cent of the patients with acute coronary occlusion had transmural infarcts, while 11% of this group showed less extensive lesions, usually limited to the subendocardial half of the left ventricular wall and the left papillary muscles. In 82% of the hearts in the group with coronary insufficiency, the infarcts were limited predominantly to the subendocardial half of the myocardium. Transmural infarcts were seen in only 18% of the cases of this group. In all the hearts of both groups a narrow zone of myocardium up to 1 mm. in thickness retaining normal staining qualities was seen immediately beneath the endocardium, regardless of the extent of the infarct. The acute infarcts limited to the subendocardial half of the cardiac wall and papillary muscles were generally

confluent. Often, however, areas of relatively normal-staining muscle were scattered in the zone of the infarcted myocardium. Usually the mass of infarcted muscle was smaller in the hearts with coronary insufficiency as compared with the infarcts in the hearts showing acute coronary occlusion.

Local Complications of Acute Myocardial Infarction (Mural Thrombosis, Myocardial Rupture, Pericarditis).—The incidence of left ventricular mural thrombi was almost identical in the two groups, occurring in more than one-third of each. Thrombi were usually adherent to the region of the infarct. However, in some cases the mural thrombus was located at the apex when the infarct did not histologically involve this region. In others it was adherent to an old infarct occurring in a portion of the ventricle removed from the acute infarct.

Extensive fibrinous pericarditis occurred in nine cases in which there was acute coronary occlusion; in each of these the infarct was transmural. Pericarditis was not seen in any of the cases in which there was coronary insufficiency, the group which predominantly had subendocardial lesions.

TABLE 4.—*Causes of Death Associated with Acute Myocardial Infarction*

	"Acute Coronary Insufficiency"		Acute Coronary Occlusion	
	Cases	% of 49 Cases	Cases	% of 94 Cases
Severe congestive failure	2	4	0	0
Ruptured myocardium	2	4	16	17
Renal failure	2	4	0	0
Pulmonary embolus	7	14	13	13
Fatal	2	4	5	5
Severe	3	6	4	4
Incidental	2	4	4	4
Bronchopneumonia	1	2	2	2
Peripheral arterial occlusion	1	2	2	2

Of particular note is the fact that of the 18 instances of rupture of the heart among the total 143 cases studied, 16 occurred in patients with acute coronary occlusion and only two in patients with coronary insufficiency. In all patients with rupture the acute infarction was transmural in distribution. Evidence of previous infarction was observed in only two hearts in which rupture had occurred. In the total series previous infarction was evident in 61% of the 143 cases. In each of the two cases in which rupture occurred and in which a healed infarct existed, the healed infarct was located in a portion of the ventricle removed from the acute infarct and rupture. The incidence of cardiac rupture in patients receiving anticoagulants was identical to that in the whole series, being 12% of 17 patients receiving adequate anticoagulant therapy as compared with an over-all incidence of rupture of 13%.

Immediate Causes of Death Associated with Acute Myocardial Infarction (Table 4).—In many instances the mechanism of death was not attributable to the myocardial infarction per se. Severe congestive failure, renal failure, pulmonary embolism, and bronchopneumonia were often considered to be mechanisms leading to death.

The incidence of pulmonary embolism was about the same in both groups. In the group with coronary insufficiency there were two instances (4%) of massive

and rapidly fatal pulmonary emboli. Similar emboli were observed in five instances (5%) in the group with acute coronary occlusion.

In two patients with acute coronary insufficiency congestive cardiac failure was the predominant picture before death. There was no complaint of precordial pain which might have led to the diagnosis of myocardial infarction. Postoperative shock was considered to be a factor in the cause of death in 10% of the cases in which there was acute coronary occlusion and in 4% of the cases in which there was coronary insufficiency.

Exclusive of cerebrovascular accidents, acute systemic arterial occlusion was thought to have contributed to death in two patients with acute coronary occlusion and in one patient with coronary insufficiency.

COMMENT

The incidence of acute myocardial infarction without acute coronary occlusion in this series is similar to that of Friedberg and Horn.[7] They stated that no coronary thrombosis was found in 31% of patients who died with acute myocardial infarction. Yater and associates,[8] on studying patients under 40 years of age, reported recent coronary occlusion in 69% of 114 hearts with gross myocardial infarction.

Lisa and Ring[9] found a low incidence (40.7%) of thrombosis in a series of 32 necropsy cases of acute myocardial infarction; Foord,[10] using a different technic of examining the coronary arteries, found a high incidence (84.6%) of thrombosis among 264 cases. The relatively high incidence of women as compared with men who died of infarction due to nonocclusive acute coronary insufficiency in this series is similar to that in the series of Gross and Sternberg,[11] in which there were eight men and seven women.

The high incidence of transmural infarction seen with acute coronary occlusion probably is explained by the sudden loss of blood supply to the area involved. It may be postulated that in coronary insufficiency, although the blood supply was severely compromised, it was not completely interrupted. The high incidence of survival of the subepicardial layers in the group with coronary insufficiency may be explained in part by the greater collateral circulation in this region of the myocardium, as demonstrated by Prinzmetal and associates.[12] The difference in character of the infarction in the two groups seems to explain the high incidence

7. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675-1679 (April 29) 1939.

8. Yater, W. M.; Traum, A. H.; Brown, W. G.; Fitzgerald, R. P.; Geisler, M. A., and Wilcox, B. B.: Coronary Artery Disease in Men 18 to 39 Years of Age: Report of 866 Cases, 450 with Necropsy Examination, Am. Heart J. **36**:334-372 (Sept.); 481-526 (Oct.); 683-722 (Nov.) 1948.

9. Lisa, J. R., and Ring, A.: Myocardial Infarction or Gross Fibrosis: Analysis of 100 Necropsies, Arch. Int. Med. **50**:131-141 (July) 1932.

10. Foord, A. G.: Embolism and Thrombosis in Coronary Heart Disease, J. A. M. A. **138**:1009-1012 (Dec. 4) 1948.

11. Gross, H., and Sternberg, W. H.: Myocardial Infarction Without Significant Lesions of Coronary Arteries, Arch. Int. Med. **64**:249-267 (Aug.) 1939.

12. Prinzmetal, M.; Bergman, H. C.; Kruger, H. E.; Schwartz, L. L.; Simkin, B., and Sobin, S. S.: Studies on the Coronary Circulation: III. Collateral Circulation of Beating Human and Dog Hearts with Coronary Occlusion, Am. Heart J. **35**:689-717 (May) 1948.

of pericarditis and cardiac rupture following acute coronary occlusion and infarction and the low incidence of these complications in the patients with coronary insufficiency. The observations on this series support the current opinion that previous infarction with scarring plays a role in preventing cardiac rupture in that part of the heart, with a subsequent acute myocardial infarct in that area.[13] In 61% of all our cases gross scarring was noted. However, of those hearts in which rupture occurred, only 11.1% showed healed infarction, and in each instance the location of the scar did not coincide with that of the acute infarct. Edmondson and Hoxie [14] reported scarring in only 26.3% of hearts with acute myocardial infarction and rupture, whereas scarring occurred in 58.4% of unruptured hearts with recent infarction. Anticoagulant therapy appeared to have had no influence on the incidence of cardiac rupture in our series. This complication occurred in 12% of those patients receiving this form of therapy and in 13% of the entire series.

The greater degree of narrowing of the anterior descending coronary artery, as compared with the other coronary arteries, may explain the fact that a higher incidence of anterior and anterolateral infarction was associated with acute coronary insufficiency than with acute occlusion. Horn and Finkelstein,[15] in studying 100 cases, noted a slightly greater degree of sclerosis in the anterior descending coronary artery than in the other main branches but did not find the difference in their series statistically significant. White and associates [16] and Ackerman and co-authors,[17] each studying the coronary arteries in 600 hearts, observed, in males [16] and in females [17] ranging from 30 to 89 years of age, a consistently greater degree of sclerosis of the anterior descending artery than of the other main branches.

As a group the hearts with coronary insufficiency and acute infarction in this series showed marked cardiac hypertrophy. This is evident not only in comparison with expected normal weight but also in comparison with a clinically similar group of cases in which there was coronary occlusion. The hearts in the latter group also showed some hypertrophy, but to a less degree. Hypertension and previous congestive failure, two factors closely related to cardiac hypertrophy, appeared to be more frequent in the patients with acute coronary insufficiency than in patients with acute coronary occlusion.

SUMMARY

A study of 143 cases of fatal acute myocardial infarction was made to determine the influence of cardiac hypertrophy on the production of acute infarction in the absence of acute coronary occlusion.

In 49 cases in which no recent coronary occlusion was observed, the average cardiac hypertrophy was 70% above normal. Approximately three-fourths of the

13. Lombardi, A. A.: Non-Traumatic Cardiac Rupture: Clinical-Pathologic Study, Thesis, University of Minnesota Graduate School, 1947.

14. Edmondson, H. A., and Hoxie, H. J.: Hypertension and Cardiac Rupture: Clinical and Pathologic Study of 72 Cases, in 13 of Which Rupture of the Interventricular Septum Occurred, Am. Heart J. **24**:719-733 (Dec.) 1942.

15. Horn, H., and Finkelstein, L. E.: Arteriosclerosis of Coronary Arteries and Mechanism of Their Occlusion, Am. Heart J. **19**:655-682 (June) 1940.

16. White, N. K.; Edwards, J. E., and Dry, T. J.: The Relationship of the Degree of Coronary Atherosclerosis with Age in Men, Circulation **1**:645-654 (April) 1950.

17. Ackerman, R. F.; Dry, T. J., and Edwards, J. E.: Relationship of Various Factors to the Degree of Coronary Atherosclerosis in Women, Circulation **1**:1345-1354 (June) 1950.

hearts in the group showed hypertrophy of at least 50% above normal. In contrast, in the 94 cases in which there was acute coronary occlusion the hearts averaged 50% over their normal predicted weight. Less than half the hearts in the latter group showed hypertrophy of at least 50% above normal.

Coronary sclerosis in the two groups appeared of equal severity. The anterior descending coronary artery in each group showed the greatest degree of narrowing.

The incidence of antecedent hypertension, cardiac failure, and old infarction, all considered to be factors leading to cardiac hypertrophy, was greater in patients with "coronary insufficiency" than in those with acute coronary occlusion.

In hearts in which no recent coronary occlusion was found, the infarct was most frequently subendocardial in distribution, and in this group there was a low incidence of cardiac rupture and pericarditis. With acute coronary occlusion, the infarct was usually transmural and there was a much higher incidence of cardiac rupture and pericarditis as compared with the group with myocardial infarction but without acute coronary occlusion. Thromboembolic complications occurred with equal frequency in the two groups.

ORAL USE OF CATION-EXCHANGE RESINS IN TREATMENT OF EDEMA

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THE SUCCESSFUL use of cation-exchange resins in the treatment of edema in man first suggested by Dock [1] has now been reported by several investigators.[2] Their use in the form of an enema for the treatment of potassium intoxication has also been reported by Elkinton and associates.[3] An excellent discussion of the mechanism of action and the many and varied uses of ion-exchange resins may be found in a monograph edited by Nachod.[4]

The purpose of the present report is to describe the use of cation-exchange resins for the removal of sodium via the intestinal tract in the treatment of edematous states and to define the advantages and limitations of this form of therapy. Both acute balance experiments showing the quantitative removal of cations in the feces and studies of the effects of prolonged administration (three months to two years) of these resins will be reported.

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From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital.

1. Dock, W.: Sodium Depletion as a Therapeutic Procedure: Value of Ion Exchange Resins in Withdrawing Sodium from the Body, Tr. A. Am. Physicians **59**:282, 1946.

2. (*a*) Greenblatt, I. J., and Gilwood, M. E.: Removal of Sodium in Vivo by Permutit Z, read before the 113th Meeting of American Chemical Society, Chicago, April 19, 1948. (*b*) Irwin, L.; Berger, E. Y.; Rosenberg, B., and Jackenthal, R.: The Effect of a Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States, J. Clin. Invest. **28**:1403, 1949. (*c*) Cobbey, T. S., Jr.; Williams, R. H.; McRae, N., and Towney, B. T.: Biochemical and Clinical Effects of Cation Exchange Resin, Federation Proc. **8**:352, 1950. (*d*) Dock, W., and Frank, N. R.: Cation Exchangers: Their Use and Hazards as Aids in Managing Edema, Am. Heart J. **40**:638, 1950. (*e*) Kahn, S. S., and Emerson, K., Jr.: Experiences with the Use of Cation Exchange Resins in the Treatment of Edema, abstracted, J. Clin. Invest. **29**:827, 1950.

3. Elkinton, J. R.; Clark, J. K.; Squires, R. D.; Bluemle, L. W., Jr., and Crosley, A. P., Jr.: Treatment of Potassium Retention in Anuria with Cation Exchange Resin, Am. J. M. Sc. **220**:547, 1950.

4. Nachod, F. C.: Ion Exchange: Theory and Application, New York, Academic Press, Inc., 1949.

MATERIAL AND METHODS

Two types of resins have been used in these studies, permutit® Z,[5] a sulfonated polystyrene-type resin, and the ammonium and potassium forms of amberlite® XE-96,[5] a cross-linked, polyacrylic (polycarboxylic) resin. Permutit® Z is a granular, reddish-black substance having the consistency of fine sand. Amberlite® XE-96 is a very fine white powder which is so light that its supplier has found it necessary to add to it an agent to facilitate its suspension in water. Both substances have a slightly dry or acrid taste which is easily disguised by any simple flavoring. We have found a few drops of lemon extract useful. The dosage of each resin has varied from 20 to 100 gm. daily in the acute experiments and from 45 to 60 gm. in prolonged treatment, given in divided amounts three or four times daily.

The following five patients were selected for quantitative studies: M. L., a 32-year-old woman with edema secondary to hypoproteinemia, resulting from a peculiar abnormal capillary permeability to protein; F. C., a 57-year-old man with edema due to arteriosclerotic heart disease and congestive failure; G. D., an 18-year-old youth with edema due to lipid nephrosis who subsequently made a complete recovery; H. A., a 56-year-old woman with diabetes, hypertension, and intercapillary glomerulosclerosis, and C. T., a 35-year-old man with hypertensive cardiovascular disease. All patients were maintained on diets containing between 500 and 800 mg. of sodium daily.

TABLE 1.—*Change in Fecal Excretion of Cations Induced by Oral Administration of Cation-Exchange Resins* **

				Sodium		Potassium		Calcium	Magnesium
Patient	Resin	Dose, Gm./ Day	Number of Days	Total, mEq./ Day	mEq./ Gm. Resin	Total, mEq./ Day	mEq./ Gm. Resin	Total, mEq./ Day	Total, mEq./ Day
M. L.	Permutit® Z	40	3	+16.0	+0.25	+24.0	+0.60	.....	.....
		60	9	+22.0	+0.37	+12.1	+0.21	.....	.....
	Amberlite® (1)†	45	9	+36.1	+0.80	+83.3	+1.85	−10.0	+0.54
	Amberlite® (2)	60	7	+33.0	+0.55	+72.0	+1.20	− 1.0	.....
	Amberlite® (2)	80	9	+27.7	+0.35	+96.0	+1.20	+ 0.2	.....
F. C.	Amberlite® (3)	25	9	+ 7.9	+0.32	+54.0	+2.16	+ 1.0	.....
	Amberlite® (3)	50	6	+15.0	+0.30	+78.0	+1.56	+ 5.0	.....
H. A.	Amberlite® (1)	45	9	+33.9	+0.75	+12.0	+0.27	− 3.0	+ 3.0
G. D.	Amberlite® (2)	40	6	+20.8	+0.52	+92.8	+2.32	± 0.0	.....
C. T.	Amberlite® (4)	60	6	+15.6	+0.26	+73.1	+1.22	.....	.....

* The values represent the increase (+) or decrease (−) in cation excretion during resin therapy as compared with excretion during a prior control period with approximately the same dietary intake.

† Amberlite® (1) was composed of approximately two-thirds of the ammonium form and one-third of the potassium form (potassium equaled 5.2%). This was resodec.® Amberlite® (2) contained equal parts of ammonium and potassium forms (potassium equaled 9.4%). Amberlite® (3) was the potassium form (potassium equaled 18.7%). Amberlite® (4) was the ammonium form.

SODIUM AND POTASSIUM EXCRETION

The extent of fecal loss of cations which may be expected to occur after administration of these resins is demonstrated in Table 1. There is a wide variation from patient to patient, and even between different periods in the same patient. From the data in Table 1 on Patients M. L. and F. C., both of whom received more than one dose-level of the same resin, no clear relation between dose and fecal cation removal can be shown. In patients receiving 40 to 60 gm. of resin a day, the total amounts of sodium removed by the resin ranged from 15.6 to 36.1 mEq., or 0.91 to 2.1 gm. of sodium calculated as sodium chloride, per day. Although rates of fecal excretion of sodium chloride exceeding 4 gm. per day have been observed during short periods of resin administration, there is a tendency for these high rates to decline to the

5. Permutit® Z was supplied by the Permutit Company of America, New York 18, and amberlite® XE-96 by Smith, Kline & French Laboratories, Philadelphia 1.

range noted in Table 1 as resin therapy is continued. These excretion rates are of the same order of magnitude as those reported by McChesney and McAuliff [6] in rats fed various types of cation-exchange resins.

The fecal excretion of potassium also varied greatly from patient to patient (Table 1). In Patient M. L. permutit® Z appeared to have less affinity for this ion than had amberlite,® which removed two to six times as much potassium as sodium per gram of resin. Interestingly enough, the amount of potassium appearing in the stools bears little relation to the form in which the resin is fed, whether it is the ammonium, potassium, or hydrogen form. It appears probable that the resin is converted completely to the hydrogen form in the acid stomach. The ammonium ion

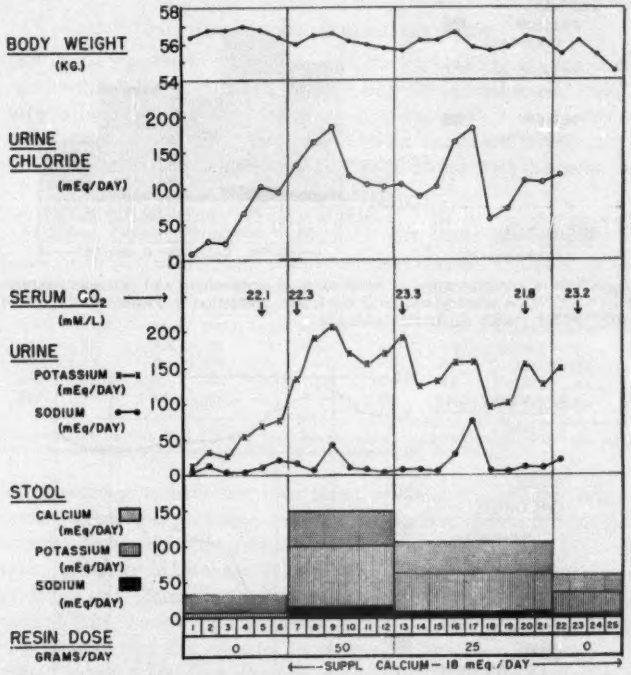

Fig. 1.—Effect of administration of amberlite® XE-96 in the potassium-saturated form on the urinary and fecal excretion of electrolytes in Patient F. C., a 57-year-old man (PBBH 8A48), with hypertensive cardiovascular disease and arteriosclerotic heart disease.

is absorbed as ammonium chloride and converted to urea. The potassium ion is also largely absorbed and mixes with the general pool of extracellular potassium, from which it may be re-excreted into the intestine and reattached to the resin as the latter reaches the alkaline mediums of the intestinal tract. If an excess of potassium is absorbed over and above the amount which can be subsequently removed by the resin, it is excreted in the urine. Figure 1 demonstrates a case in which a potassium-

6. McChesney, E. W., and McAuliff, J. P.: Effects of Some Ion Exchange Resins on the Mineral Metabolism of Rats, Am. J. Physiol. **160**:264, 1950.

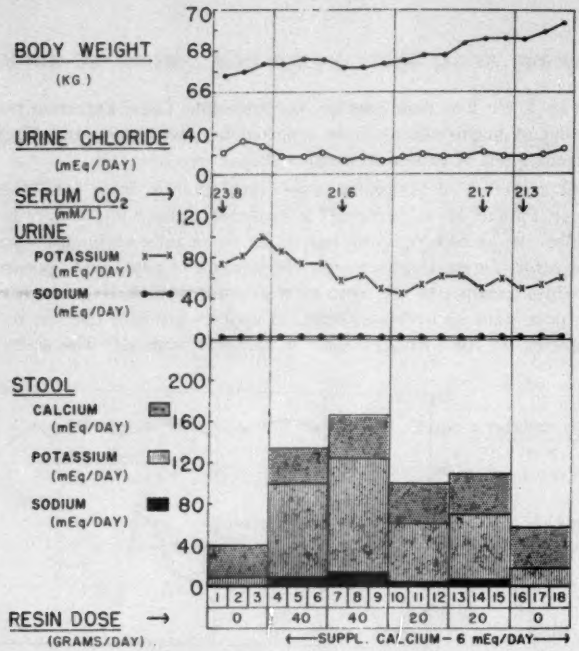

Fig. 2.—Effect of administration of equal parts of ammonium- and potassium-saturated forms of amberlite® XE-96 on urinary and fecal electrolyte excretion in Patient G. D., an 18-year-old boy (PBBH P9205), with nephrotic syndrome.

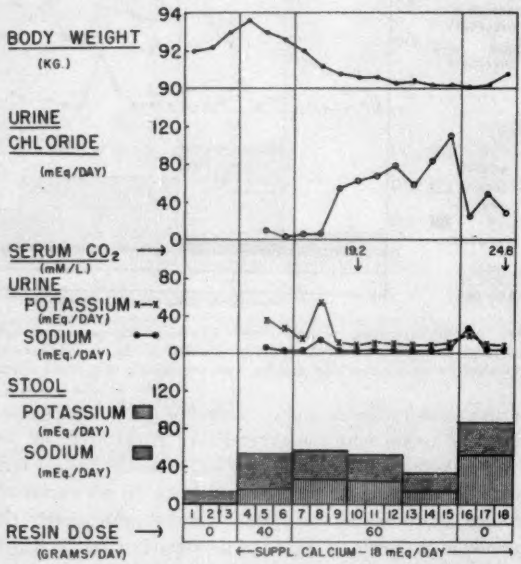

Fig. 3.—Effect of administration of a hydrogen-saturated resin, permutit® Z, on the urinary and fecal excretion of electrolytes in Patient M. L., a 32-year-old woman (PBBH 5A246), with idiopathic edema.

saturated form of resin was fed, containing 18.7% potassium by weight or 4.8 mEq. per gram. The striking increase in urine potassium is apparent and accounts for nearly half of the potassium initially contained on the resin. When equal parts of ammonium and potassium forms of resin are fed, urinary potassium remains constant (Fig. 2), indicating that the extra potassium ingested is approximately equal to that eventually adsorbed on the resin in the intestine. When permutit® Z is fed in the hydrogen form, urinary potassium falls sharply to minimal values in order to compensate for the excess fecal loss (Fig. 3). A comparison of Figures 1 and 2 reveals that as much, or more, potassium appeared in the stools when the amberlite® resin was only half saturated with potassium as when it was fully saturated, that is, when the patient ingested twice as much potassium.

CALCIUM AND MAGNESIUM EXCRETION

In spite of the greater in vitro affinity of the carboxyl resins for calcium and magnesium ions than for monovalent ions, the increase in fecal loss of these bivalent ions in vivo is much smaller than the increase in fecal loss of the monovalent ions (Table 1). It may be presumed that these bivalent metals are largely in unionized form in the intestine, and hence unavailable for combination with the resin. Although

TABLE 2.—*Complete Balance Study Showing Effect of a Mixture of the Ammonium and Potassium Forms of Amberlite® XE-96 Resin on Electrolyte Excretion* *

Period (5 Days)	Resin, Gm./ Day	Sodium, mEq./Day			Potassium, mEq./Day			Calcium, mEq./Day			Magnesium, mEq./Day		
		Stool	Urine	Balance	Stool	Urine	Balance	Stool	Urine	Balance	Stool	Urine	Balance
I	0	1.0	6.0	+27.8	12	73	+37	44.1	5.9	+15.0	10.7	8.8	+12.7
II	45	71.0	2.9	—39.1	73	77	—40	61.0	5.1	— 1.1	13.0	5.1	+13.5
III	45	30.0	8.7	— 3.9	46	55	+19	23.5	7.4	+23.7	9.1	3.5	+19.6
IV	45	10.4	0.8	+23.6	167	34	—91	17.1	6.1	+41.8	23.2	1.2	+ 0.8

* This study was made of Patient M. L., a 32-yr.-old woman, with idiopathic edema. The daily intake of sodium was 84.8 mEq.; of potassium, 110 mEq.; of calcium, 65 mEq., and of magnesium, 32.2 mEq.

fecal iron measurements have not been made, no evidence of iron deficiency has been observed, even after prolonged resin administration, indicating that this metal, too, is largely unavailable to the resin.

A typical complete balance study employing a mixture of the ammonium and potassium forms of amberlite® XE-96 is presented in Table 2. It will be noted that in this patient with a constant low-sodium intake a negative sodium balance was achieved, indicating that it is possible to remove sodium from the body as well as from ingested food. A transient negative calcium balance occurred during only the first three days of resin administration, which was followed by an increased calcium absorption. The slight increase in fecal magnesium was largely offset by a decrease in urinary excretion, so that a positive magnesium balance was maintained.

Greenblatt and Gilwood [28] have reported the production of hypocalcemia and tetany following the prolonged use of permutit® Z in one patient. We have had a similar experience in Patient M. L., in whom hypocalcemia and hypokalemic alkalosis developed simultaneously after six weeks' treatment with permutit® Z in increasing doses up to 100 gm. daily (Fig. 4). After a period of rapid weight loss, she suddenly displayed marked weakness, generalized muscular cramps, nausea, vomiting, and cardiac arrhythmias. The resin treatment was immediately discontinued, and vigorous replacement therepy was instituted. In spite of this, the serum

calcium and potassium levels continued to fall for another three days, perhaps indicating the time required for the resin to pass out of the intestine. Thereafter the patient recovered uneventfully. Curiously enough, her serum sodium concentration never fell significantly below normal, although she had been maintained on a low-salt intake throughout the study.

These observations indicate the necessity of supplying extra potassium and calcium in the diet to prevent the development of deficiencies of these ions. In pro-

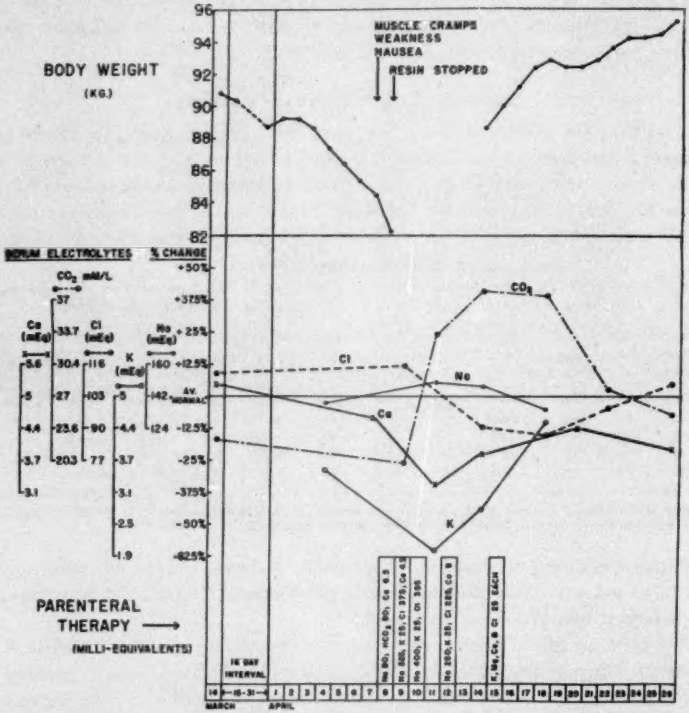

Fig. 4.—Induction of hypocalcemia and hypokalemic alkalosis by the administration of large doses of a sulfonated cation-exchange resin in the hydrogen form (permutit® Z) without adequate supplementation with potassium and calcium in patient M. L., a 32-year-old woman (PBBH 5A246), with idiopathic edema. Permutit® Z resin was administered in the following dosages: 60 gm. daily, Feb. 18 to 28; no resin, March 1 to 4; 60 gm. daily, March 5 to 16; 75 gm. daily, March 17 to 29; 100 gm. daily, March 30 to April 7.

longed treatment we have employed an ammonium form of amberlite® resin to which a sufficient amount of the potassium form has been added to supply 60 mEq. of potassium in the standard daily dose of 45 gm. (5.2% potassium by weight).

With this form of resin we have encountered no definite clinical signs of calcium or potassium deficiency; nevertheless, as will be noted later, a gradual depletion of body potassium may occur during prolonged administration of this resin. It is

advisable to supply extra amounts of both calcium and potassium if continuous therapy is carried out for long periods. The daily administration of 0.5 gm. of dicalcium phosphate and 1.5 gm. of potassium chloride should be adequate.

TABLE 3.—*Effect of Ammonium Form of Amberlite® XE-96 on Urinary Urea and Ammonia Excretion in a Patient with Nephrotic Syndrome but Normal Renal Function* *

Date	Resin, Gm./Day	Urea Nitrogen, Gm./Day	Ammonia Nitrogen, mEq./Day	Blood Urea Nitrogen, Mg./100 Cc.
11/28	..	2.4	4.3	22
11/29	..	3.6	3.6	20
11/30	..	5.2	0.3	19
12/ 1	50	5.6	14.3	22
12/ 2	50	6.9	28.6	21
12/ 3	50	7.3	40.1	22
12/ 4	50	4.0	98.0	18
12/ 5	50	4.6	56.5	..
12/ 6	..	4.5	47.8	..
12/ 7	..	5.2	49.3	..
12/ 8	..	4.4	39.3	..
12/10	..	4.23	33.5	..

* This study was made on Patient G. D., an 18-yr.-old youth, with nephrotic syndrome. Note tenfold increase in urinary ammonia. No acidosis developed during a subsequent three-month period of continuous resin therapy.

TABLE 4.—*Effect of Ammonium Form of Amberlite® XE-96 on Urinary Urea and Ammonia Excretion and Electrolyte Balance in Patient P. P. with Marked Renal Insufficiency* *

Date	Resin, Gm./Day	Urea Nitrogen, Gm./Day	Ammonia Nitrogen, mEq./L.	Blood Urea Nitrogen, Mg./100 Cc.	Sodium, mEq./L.	Potassium, mEq./L.	Chloride, mEq./L.	Carbon Dioxide, mM./L.
2/ 3	..	6.1	0.05	...	...	...	...	....
2/ 4	..	2.2	0.1	110	134	8.0	108	19.3
2/ 5	..	4.1	0.2	...	...	...	...	....
2/ 6	..	2.6	0.05	108	138	10.0	106	....
2/ 7	0	4.3	0.1	...	135	8.3	...	....
2/ 8	0	3.2	0.05	117	138	9.0	104	19.8
2/ 9	0	4.3	0.1	...	...	...	...	....
2/10	30	2.8	0.1	...	138	8.8	...	....
2/11	30	2.0	0.1	...	...	...	...	....
2/12	50	1.2	0.05	...	...	...	...	....
2/13	50	2.4	2.2	...	132	6.5	...	....
2/14	0	2.6	2.7	...	...	...	...	....
2/15	0	2.4	3.8	115	128	6.0	96	14.0
2/16	0	1.6	3.3	...	...	...	...	....

* Patient P. P. was a 46-yr.-old man, with chronic glomerulonephritis. Note lack of significant rise in ammonia excretion and marked fall in serum carbon dioxide-combining power. Of interest also is the sharp fall in the toxic levels of the serum potassium following resin therapy.

ACIDOSIS

As first pointed out by Irwin and associates,[2b] the excess loss of base from the body via the intestinal tract during resin administration requires a compensatory increase in excretion of acid and ammonia in the urine to prevent systemic acidosis. It naturally follows that resin therapy is contraindicated in patients with a sufficient degree of renal damage to impair ammonia formation and the ability to excrete an acid urine. Fortunately, these functions are maintained even in the presence of moderately severe renal damage, but the development of acidosis must be carefully

watched for in all patients showing any sign of renal disease and is the most important limiting factor in the therapeutic use of resins. When presence of renal disease is suspected, we have used the measurement of urinary ammonia as an indication of whether or not to continue resin therapy. Tables 3 and 4 show examples of urinary ammonia excretion in response to resin therapy. Patient G. D. (Table 3) was an 18-year-old youth with characteristic findings of the nephrotic syndrome, but showing normal renal function except for proteinuria. His kidneys were able to achieve a tenfold increase in ammonia production, and no sign of acidosis developed even during a subsequent three months' course of continuous resin therapy. Patient P. P. (Table 4), on the other hand, with severe glomerulonephritis was unable to form ammonia, and acidosis rapidly developed, necessitating withdrawal of resin therapy. It is of some interest to point out the marked reduction in his elevated serum potassium level following administration of the ammonium form of resin, a finding which Elkinton [8] has taken advantage of in the treatment of potassium intoxication.

For practical purposes the determination of the carbon dioxide-combining power at frequent intervals during the early phase of resin therapy is sufficient to discover a deficient renal compensatory mechanism in time to prevent serious consequences. Nevertheless, all patients should have a thorough evaluation of renal function, including urinalysis and determination of phenolsulfonphthalein excretion and blood urea or nonprotein nitrogen level before undertaking resin therapy.

PROLONGED USE OF AMBERLITE® XE-96

For periods ranging from six months to two years six patients have been treated continuously with a mixture of the ammonium and potassium forms of amberlite® XE-96.[7] Except in the cases indicated, 15 gm. of the resin was administered three times daily. During the first three months of treatment complete blood-electrolyte studies were performed every two weeks or oftener. Brief protocols of these patients follow:

J. W., a 50-year-old white woman, first noted onset of dyspnea, palpitation, and ankle edema in 1946. A diagnosis of rheumatic heart disease, with mitral stenosis and insufficiency, cardiac insufficiency, and auricular fibrillation was made in 1947, and the patient was treated with digitalis, a low-salt diet, ammonium chloride, and meralluride injection ("mercuhydrin" sodium solution), 2.0 cc. twice a week. The patient did fairly well, except for three episodes of cerebral embolism and frequent digitalis toxicity. Resin therapy was begun April 4, 1950; ammonium chloride and meralluride therapy was discontinued at that time, and the patient has done well. During the three-month trial period, her weight has varied from 138 to 144 lb. (62.6 to 65.3 kg.), vital capacity from 1,000 to 1,550 cc. Hematocrit varied from 38 to 47. Blood urea nitrogen on one occasion was reported as 31 mg. per 100 cc. but did not rise above 15 mg. per 100 cc. on any other occasion. Potassium has varied from 3.8 mm. to 4.9 mEq., sodium, from 132 to 144 mEq., calcium, from 4.8 to 5.7 mEq., and chloride, from 94 to 110 mEq., per liter. The carbon dioxide-combining power varied from 18.8 to 23.4 mM. per liter. She received no mercurial drugs after the second week of therapy and is free of edema, with dyspnea on exertion only.

J. G., a 73-year-old white man, has been followed in the outpatient department since 1938, with the diagnosis of bronchiectasis, arteriosclerotic heart disease, probable mild Laennec's cirrhosis, and pernicious anemia. He received digitalis, a low-salt diet, ammonium chloride, and mercurial diuretics intermittently in that time. This regimen was last begun Jan. 31, 1950, because of mild cardiac decompensation. With this regimen weight slowly fell from 196 to 184 lb. (88.9 to 83.5 kg.), and vital capacity ranged from 2,800 to 3,000 cc. Mercurial diuretics

7. These forms were supplied as resodec® by Smith, Kline & French Laboratories, Philadelphia 1.

were given every two weeks. Resin therapy was begun Nov. 15, 1950, and the only other therapy since that time has been digitalis, salt restriction, and liver extract. During the next three months, his weight slowly dropped to 180 lb. (81.6 kg.); vital capacity ranged from 2,600 to 3,000 cc., and hematocrit, from 47 to 40. Serum potassium varied from 4.0 to 4.3 mEq., sodium, from 136 to 148 mEq., calcium, from 4.7 to 5.5 mEq., and chloride, from 105 to 111 mEq., per liter. The carbon dioxide-combining power ranged from 19.8 to 25.1 mM. per liter. The patient has done well symptomatically. He has little dyspnea, a trace of dependent edema intermittently, and some complaints of weakness. This patient is of particular interest in that he had no free gastric hydrochloric acid. Apparently, in spite of this his gastric pH was low enough to activate the resin by replacing ammonium and potassium with hydrogen ions.

S. J., a 58-year-old white man, was first seen Sept. 10, 1948, with left pleural effusion and splenomegaly of undetermined origin. In January, 1949, exploratory laparotomy for progressive painless ascites revealed metastatic carcinoma of the pancreas. In April, 1950, he began to experience orthopnea and exertional dyspnea with occasional substernal oppression. He was digitalized and given a low-salt diet and mercurial diuretics with excellent response. Cardiac failure was felt to be on an arteriosclerotic basis. Edema and ascites were controlled by mercurial and digitalis treatment from that time until September, 1950, at which time resin therapy was begun. During the three-month trial period, his weight has slowly decreased from 164 to 156 lb. (74.4 to 70.8 kg.); vital capacity, which was 1,800 cc. at the beginning of treatment, rose to 2,100 cc.; hematocrit has varied from 42 to 45. Serum potassium has ranged from 3.6 to 5.3 mEq.; serum sodium, from 138 to 148 mEq.; calcium, from 4.9 to 5.7 mEq., and chloride, from 97 to 115 mEq., per liter. The carbon dioxide-combining power ranged from 20.3 to 25.7 mM. per liter. The patient has done quite well symptomatically, and edema and ascites are under good control.

T. A., a 68-year-old white man, was first seen July 7, 1950, in cardiac failure on the basis of coronary-artery arteriosclerosis and chronic bronchitis. The patient was digitalized, given ammonium chloride, a low-salt diet, and meralluride injection twice a week. In two weeks his weight had dropped from 188 to 182 lb. (85.3 to 82.6 kg.), and he was doing fairly well subjectively. He still occasionally complained of muscle weakness and cramps after taking mercurial drugs. Resin therapy was begun Aug. 25, 1950, and his weight immediately dropped from 182 to 177 lb. (82.6 to 80.3 kg.), despite previous adequate diuretic therapy. Since that time the patient has received only resin, a low-salt diet, and digitalis. He has maintained his weight at 178 to 181 lb. (80.7 to 82.1 kg.) and his vital capacity at 2,800 to 3,000 cc. He has no dyspnea or dependent edema. During the three-month trial period, the potassium varied from 4.0 to 4.9 mEq.; serum sodium, from 138 to 149 mEq.; calcium, from 4.5 to 5.5 mEq., and chloride, from 100 to 113 mEq., per liter. The carbon dioxide-combining power was 17.6 to 24.7 mEq. per liter. Hematocrit was 44 to 46, and blood urea nitrogen, 14 mg. per 100 cc.

K. S., a 58-year-old married woman, was admitted to the Peter Bent Brigham Hospital on March 10, 1950, because of exertional dyspnea, progressive swelling of the legs, and precordial pain of two years' duration. She had had known hypertension and diabetes for 10 years. Increasingly frequent injections of mercurials were required to control the edema. Physical examination revealed a blood-pressure reading of 240/120 mm. Hg. There was 3+ edema of the lower part of the legs. The heart was enlarged, and there was a diastolic gallop. The liver was enlarged 6 cm. below the costal margin. The blood urea nitrogen was 10 mg.; serum protein, 6.5 gm., and fasting blood sugar, 130 mg., per 100 cc. The serum chloride was 93 mEq., and the carbon dioxide-combining power, 24.4 mM. per liter. Phenolsulfonphthalein excretion was 15% in 15 min. and 50% in two hours.

The patient was given a low-salt diet and cation-exchange resin, 45 gm. per day. She gradually lost all but traces of her edema, and her liver returned to normal size without further mercurial therapy. After nine months of resin therapy, her serum sodium was 140 mEq.; potassium, 4.5 mEq.; calcium, 4.8 mEq.; chloride, 100 mEq., and carbon dioxide-combining power, 25.5 mM., per liter. The blood sugar was 153 mg., serum cholesterol, 335 mg., and hemoglobin, 12.35 gm., per 100 cc. At this time her blood pressure had fallen to 185/95 mm. Hg. She then discontinued the resin treatment of her own accord, and therapy with mercurial

diuretics was reinstituted by her local physician. Three months later her blood pressure had risen to 260/130 mm. Hg, although her edema was fairly well controlled.

M. L., a 32-year-old female graduate nurse, was first admitted to the Peter Bent Brigham Hospital, Dec. 10, 1945, because of progressive generalized edema of five months' duration without apparent cause. On examination the patient was found to be obese, orthopneic and dyspneic. Massive subcutaneous edema of the lower extremities extending to the waist, marked puffiness of the face, bilateral pleural effusions, and a small amount of free fluid in the abdomen were present. The blood pressure was 125/80, and the results of the physical examination were otherwise normal. Extensive studies revealed no laboratory evidence of cardiac, renal, or hepatic disease. Serum protein values ranged between 5 and 6 gm. per 100 cc., with a normal albumin to globulin ratio. Electrophoretic analysis, however, revealed low serum albumin and elevated alpha globulin levels. There was no clinical sign of hypothyroidism, and a trial of thyroid administration produced no improvement.

Treatment consisted of frequent chest taps and use of numerous diuretics. Mercurial drugs were administered with partial relief of edema, until the patient began to experience severe febrile reactions after each injection, and they could no longer be given. An intensive trial of human albumin therapy produced an excellent diuresis at first, but after two weeks edema fluid began to reaccumulate in spite of continued administration of albumin. At this point analysis of the subcutaneous fluid removed from the patient's legs revealed a protein content of 3.5 gm. per 100 cc., almost entirely albumin. It became apparent that this patient was suffering from a generalized abnormal capillary permeability to protein, a condition unique in our experience.

During the next two years the patient was more or less incapacitated by her edema. She was frequently hospitalized for Southey-tube drainage, with temporary partial relief only.

In February, 1949, the first quantitative studies of sodium removal by resins which have been described above were carried out (cf. M. L., Tables 1 and 2). Since that time the patient has been treated almost constantly with resins, receiving for most of this time 45 to 75 gm. of the mixture of the ammonium and potassium forms of amberlite® XE-96 daily in conjunction with a low-salt diet. Although she still shows considerable edema, her weight has been kept 30 to 40 lb. (13.6 to 18.1 kg.) lower than before resin treatment, and she has been much less incapacitated. After 18 mo. of treatment she began to complain of mild weakness and muscle cramps. Her serum electrolyte levels were entirely normal, but withdrawal of resin therapy for a few days resulted in prompt disappearance of her symptoms. The most recent studies, in February, 1951, have revealed per liter of serum, 144 mEq. of sodium, 4.8 mEq. of potassium, 5.3 mEq. of calcium, 109 mEq. of chloride, and a carbon dioxide-combining power of 21.7 mM.

After two years of resin therapy this patient's condition was reevaluated in the hospital. Measurement of extracellular fluid by the thiosulfate method,[8] of the total body water with deuterium oxide,[9] and of the total miscible body sodium and potassium by the isotope-dilution method[10] were carried out by Dr. I. S. Edelman, Dr. A. H. James, Dr. H. B. Haley, and Dr. R. H. Cardozo, of the Department of Surgery, Peter Bent Brigham Hospital, through the kindness of Dr. Francis D. Moore. The analyses revealed that during the two years of resin administration this patient had increased her total body sodium by approximately 500 mEq. and reduced her total body potassium by the same amount.

This interesting observation brings out two important facts. First, even prolonged administration of amberlite® XE-96 in conjunction with a low-sodium intake did not produce depletion of body sodium in this patient. Second, some depletion of intracellular potassium had apparently occurred in this time with replacement

8. Cardozo, R. H., and Edelman, I. S.: To be published.

9. Schloerb, P. R.; Friis-Hansen, B. J.; Edelman, I. S.; Solomon, A. K., and Moore, F. D.: The Measurement of Total Body Water in the Human Subject by Deuterium Oxide Dilution, with a Consideration of the Dynamics of Deuterium Distribution, J. Clin. Invest. **29**:1296, 1950.

10. Moore, F. D.: Determination of Total Body Water and Solids with Isotopes, Science **104**:157, 1946.

by sodium. The daily administration of 1.5 gm. of potassium chloride as enteric-coated tablets has enabled this patient to maintain resin therapy continuously without the appearance of weakness and muscle cramps.

In all these patients the resin therapy has been well tolerated and has controlled the edema either partially or completely. In cases in which repeated mercurial injections were required before treatment, they no longer were necessary thereafter. All these subjects preferred resin therapy to mercurial diuresis because it provided a slow gradual weight loss and continuous control of the edema rather than the rapid fluctuation in water balance induced by mercury, with its concomitant symptoms of weakness, lassitude, and depression. We have not attempted to increase the salt content of the diet because we have felt that 2 gm. is approximately the maximum daily quantity that it is practicable to remove over prolonged periods by means of resins. This maximum is not yet definitely established, however; other workers using permutit® Z report up to 5 gm. daily of sodium calculated as sodium chloride recovered in the stools.[28]

Resin therapy has been unsuccessful in three additional patients in whom we have tried it. One of these was a patient with portal cirrhosis in whom resin induced nausea and anorexia, and its use had to be discontinued to prevent further nutritional deficiency and liver damage. Another was a woman with diabetes, hypertension, and intercapillary glomerulosclerosis. She presented massive edema and had become refractory to mercurials. After two weeks of resin therapy she lost 20 lb. (9.1 kg.), but her serum carbon dioxide-combining power had fallen to 15 mM. per liter, and nausea and vomiting developed, necessitating discontinuation of resin administration. Thereafter, however, her edema responded once more to mercurial therapy. A third patient was forced to stop the use of resin because of severe constipation.

OTHER USES

Preliminary studies indicate that cation-exchange resins may be of value in the control of obesity. We have been able to remove 10 to 15 lb. (4.5 to 6.8 kg.) of body weight from two patients with marked obesity after they had failed to show further weight loss on an 800-calory diet. In these patients the resins had the added advantage of reducing appetite.

In the treatment of premenstrual edema, resin therapy may have a useful place. Thus far, one patient so treated lost rather than gained weight premenstrually and failed to show her usual signs of premenstrual tension. In two other patients premenstrual weight gain has been prevented by administration of resins for two weeks prior to menstruation.

An investigation of resin therapy in the edema of pregnancy is now under way, with the co-operation of members of the staff of the Boston Lying-in Hospital. Particular care is being taken to exclude patients with toxemia and other renal complications, and, as yet, no conclusions regarding the value of resins during pregnancy have been reached.

Obviously, a long-term study of resin therapy in hypertension is of great importance in order to compare its efficacy with that of other forms of salt restriction.

The successful treatment of acute potassium intoxication by the rectal administration of an ammonium form of the resin, as reported by Elkinton,[3] has already been mentioned. We have tried this procedure in two cases of terminal uremia with hyperkalemia using the ammonium form of amberlite® XE-96. Fifty grams sus-

pended in 150 cc. of tap water was instilled daily per rectum and retained as long as possible. In one patient a total of 30.51 mEq. of potassium was removed via the intestine during a three-day period, and in the same time the serum potassium fell from 8.5 to 5.3 mEq. per liter. The patient showed temporary improvement but died one month later as a result of his renal disease. The second patient was treated similarly, and his serum potassium level fell from 9.0 to 5.8 mEq. in three days. There was no essential clinical improvement, however, and he died two days later. Nevertheless, in patients with reversible anuria this procedure might well be life-saving.

When the administration of an enema of the ammonium resin is contemplated for the removal of potassium from a patient receiving digitalis, the use of digitalis should be discontinued for several days beforehand. This precaution was pointed out recently by Merrill,[11] who showed that potassium protects against digitalis toxicity and that a nontoxic dose of digitalis may become toxic when the serum potassium level is reduced.

COMMENT

It is apparent from the above data and that of others that the oral administration of resins provides a safe and reasonably practical way of removing significant quantities of salt from the body in patients with adequate renal function. Although cation-exchange resins are capable of combining with basic amino acids and certain basic vitamins in vitro, no evidence of either protein or vitamin deficiencies has appeared after prolonged administration of these substances in human beings. Similar prolonged feeding experiments in rats have shown no interference with growth and no detectable change in nitrogen balance.[6] Inorganic cations have a greater affinity for resins than these organic bases, and it seems probable that the high sodium concentration in the intestine prevents their combination with the resin to any appreciable degree.

At present the principal drawback to resin therapy is the inconvenience of the relatively large amounts of material which must be ingested daily. This becomes the limiting factor in the quantity of sodium which can be removed, and, until resins with still higher sodium-combining capacities are developed, it is our opinion that they should be considered as an adjunct to, rather than a substitute for, a low-salt diet. We suggest that for practical purposes, when resin therapy is started the patients be maintained on a low-salt diet. If they are successfully maintained free of edema, their salt intake may be cautiously increased until they begin to show signs of water retention. Of course, if it is desired to increase the salt intake above this level, mercurial diuretics may be employed in conjunction with the resins, which enhance the diuretic effect of mercury just as does ammonium chloride.

Since most resins remove more potassium than sodium, 60 mEq. or 2.33 gm., of potassium is incorporated in the 45-gm. daily dose of the resin used in these long-range studies. Based on our experience with one patient (M. L.), the additional administration of 1 to 2 gm. of potassium chloride may prove advisable. By this means also some potassium is made available for excretion by the kidneys, thereby helping to combat the tendency to systemic acidosis. Although we have not observed

11. Merrill, J. P.; Weller, J. M.; Criscitiello, M. G.; Levine, H. D., and Lown, B.: Effect of Serum Cation Concentration upon Electrocardiographic Abnormalities, read before the Boston Chapter of the American Federation for Clinical Research, Boston, April 16, 1951.

calcium or magnesium deficiencies during prolonged administration of amberlite® XE-96, the possibility of the occurrence of such deficiencies must be constantly kept in mind. If these precautions are observed and at the same time weekly determinations of the serum carbon dioxide-combining power are made during the first two or three weeks of treatment to forestall acidosis, we believe that resin therapy may safely be carried out on an ambulatory basis for indefinite periods.

SUMMARY

The oral administration of cation-exchange resins for the removal of sodium from the intestinal tract in patients with edema has been investigated and found to be a practical and useful procedure.

The amount of sodium removed is variable, ranging from 0.25 to 0.8 mEq. per gram of resin, sometimes reaching higher levels for short periods. The total quantity removed is only partly dependent on the sodium ingested, and it is possible to remove sodium from body fluids and thereby to achieve a negative sodium balance. For practical purposes a daily dose of 45 gm. may be expected to remove approximately 2 gm. of sodium chloride, although the figure will vary considerably above and below this level in individual patients. Larger doses may be given but are likely to be poorly tolerated because of their bulk.

Since most resins remove more potassium than sodium, at least 1.3 mEq. of potassium (equivalent to 0.1 gm. of potassium chloride) must be supplied per gram of resin administered. This may be incorporated in the resin itself. It is probably also advisable to give small amounts of extra calcium.

Resin therapy should not be employed in patients with significant degrees of renal insufficiency. The loss of base in the feces must be compensated for by renal ammonia and acid production, or systemic acidosis will result.

Other clinical uses for cation-exchange resins are suggested.

The advantage of resin therapy lies in the fact that it produces a slow, steady withdrawal of sodium over prolonged periods without the sudden fluctuations induced by most diuretics. The disadvantages lie in the large quantity of material which must be ingested daily, with the possibility of gastric irritation, and in the danger of inducing acidosis in patients with renal disease, or potassium depletion if sufficient supplementary potassium is not provided.

Dr. James P. O'Hare and Dr. George W. Thorn assisted and advised in this study. Miss Grace Lincoln gave technical assistance.

SUBCLINICAL INFECTIOUS MONONUCLEOSIS WITH HEPATITIS

Epidemic in a Class of One Hundred Two Medical Students; A Two-Year Study

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THE HIGH prevalence of infectious mononucleosis, especially among the school and army population and young medical personnel, is well attested to by a voluminous literature on the subject.[1] In addition to sporadic cases, numerous clinical epidemics have been reported since the first description by West [2] in 1896 of one in a community in Ohio. However, Halcrow,[3] in a study of an epidemic of 296 cases in an Emergency Medical Service Hospital in Scotland in 1942, was the first to emphasize the occurrence of cases with hematoserologic evidences of infectious mononucleosis without the usual clinical manifestations. Vander Meer and associates [4] found 340 subclinical cases in an army camp in Wisconsin within a five-month period. Wechsler and associates [5] reported an epidemic in an army post in Texas of 556 cases, of which 112 lacked clinical findings. Since infectious mononucleosis is not usually reported to public-health authorities, its true incidence can only be surmised. The extent of additional subclinical cases has not been thoroughly explored and may add considerably to the true incidence.

It is the purpose of this paper to give the evidence for subclinical infectious mononucleosis occurring in epidemic form in a class of 102 medical students in the spring of 1949. This epidemic had additional significance because of the high percentage of abnormal results on liver-function tests persisting for two years. In the past decade there has been increasing interest in the high incidence of hepatitis

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1. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85, 1940.

2. West, J. P.: Epidemic of Glandular Fever, Arch. Pediat. **13**:889, 1896.

3. Halcrow, J. P.; Owen, L. M., and Rodger, N. O.: Infectious Mononucleosis with an Account of an Epidemic in an E. M. S. Hospital, Brit. M. J. **2**:443, 1943.

4. Vander Meer, R.; Lutterloh, C. H., and Pilot, J.: Infectious Mononucleosis: An Analysis of 26 Clinical and 340 Subclinical Cases, Am. J. M. Sc. **210**:765, 1945.

5. Wechsler, H. F.; Rosenblum, A. H., and Sills, C. T.: Infectious Mononucleosis: Report of an Epidemic in an Army Post, Ann. Int. Med. **25**:113 and 236, 1946.

occurring in clinical infectious mononucleosis in the absence of jaundice.[6] This may be as high as 90%. However, this is the first study of the evidence of hepatitis in subclinical infectious mononucleosis. Because of the benign clinical manifestations, the persistence of abnormal reactions to liver-function tests 22 mo. later was quite unexpected. In view of possible etiological relationships to the later development of Laennec's cirrhosis,[7] this deserves thought and further study.

DESCRIPTION OF THE EPIDEMIC

In the spring of 1949 there was an unusually large number of clinical cases of infectious mononucleosis in Brooklyn, as well as in many other cities in the East, particularly in schools and colleges.[8] At this time the 102 second-year medical students at the Long Island College of Medicine, as part of the routine assignment in the course in laboratory diagnosis, were engaged in performing white-blood-cell differential counts on their own blood. There was immediate consternation and confusion regarding the identification and differentiation of lymphocytes and monocytes, unusual even for second-year students. The explanation became evident when about a quarter of the class members were found by us to have a significant number of typical Downey cells. An investigation of the entire class for further evidence of infectious mononucleosis was then undertaken.

This seemed to be of particular interest because it involved a study of 102 students who were supposedly in good health, as tacitly inferred from the mere fact of their presence in class. Many difficulties were obviously apparent, chief among them the lack of a single specific diagnostic test. However, since the majority of persons with this disease will show a positive heterophile-antibody titer, positive cephalin-flocculation and thymol-turbidity reactions, and the presence of Downey cells, especially if followed at frequent intervals, the diagnosis may be advanced by a combination of positive reactions to tests. Ideally these tests should be carried out at least once a week for four weeks for the highest number of positive findings. Since this was not feasible in such a large number of cases, a compromise was made for two complete surveys spaced three weeks apart. In the complete follow-up study four months later—the students now being in the third year of medical school—many of the test reactions were still abnormal. Therefore, those students with positive findings were followed at the 6th, 9th, 12th, and 22d mo., or until the data became normal. On the last follow-up study at 22 mo., at the end of the fourth year of medical school, there were still some abnormal reactions.

METHOD AND MATERIALS

1. *Downey Cells.*—Differential counts of the white blood cells were done by us on cover slips stained with Wright's stain. It was especially important to have rigid criteria for Downey cells, since the point at which a lymphocyte becomes sufficiently atypical to be called a Downey

6. DeMarsh, Q. B., and Alt, H. L.: Hepatitis Without Jaundice in Infectious Mononucleosis, Arch. Int. Med. **80**:257 (Aug.) 1947. Angle, R. M.: Hepatitis Without Jaundice in Infectious Mononucleosis, Gastroenterology **12**:617, 1949. Bennett, H. D.; Frankel, J. G.; Bedinger, P., and Baker, L. A.: Infectious Mononucleosis with Hepatitis, Arch. Int. Med. **86**:391 (Sept.) 1950.

7. Leibowitz, S., and Brody, H.: Cirrhosis of the Liver Following Infectious Mononucleosis, Am. J. Med. **8**:675, 1950.

8. Evans, A. S., and Robinton, E. D.: An Epidemiologic Study of Infectious Mononucleosis in a New England College, New England J. Med. **242**:492, 1950.

cell is somewhat a matter of personal evaluation. Slightly atypical cells were, therefore, disregarded, and a cell was classified as a Downey cell if it possessed abundant vacuolated cytoplasm, marked indentation of the nucleus, or fenestration or chromatin coarsening of the nucleus. The presence of 3% or more of these cells was considered an abnormal finding.

2. *Clinical Examination.*—Each student was individually questioned concerning any symptoms suggestive of infectious mononucleosis and was examined for the presence of pharyngitis, lymphadenopathy, or icterus.

3. *Heterophile Titer.*—The Davidsohn [9] test was the one employed, since this is more specific for infectious mononucleosis than the Paul-Bunnell test. Our procedure included a microscopic reading of the tubes with a low-power objective. The test consists of differential absorption of the patient's serum with a suspension of guinea-pig kidney and with boiled ox erythrocytes, with a determination of the sheep-cell agglutination titer before and after absorption.[10] The agglutinins in infectious mononucleosis are absorbed by beef erythrocytes, but not by guinea-pig kidney, and a titer of 1:28 or more after absorption by guinea-pig kidney is considered highly diagnostic for infectious mononucleosis.[11] In fact, some consider a titer as low as 1:14 significant.

4. *Cephalin Flocculation.*—Hanger's method,[12] as modified by Neefe and Reinhold, was followed. The cephalin-cholesterol mixture prepared by Wilson Laboratories, Chicago, was used. Since this antigen in our hands is less sensitive, a 1+ reaction is considered suggestive, and a 2+ result, abnormal.

5. *Thymol Turbidity.*[13]—Five units or more was considered abnormal.

6. *Sulfobromophthalein (Bromsulphalein®) Sodium Excretion.*—At four months, the 33 students who had been found to have elevated thymol and cephalin-flocculation values were given the test with sulfobromophthalein sodium, using 5 mg. of the dye per kilogram of body weight given intravenously, with collection of samples at 0 and 45 min. Normally there is less than 5% retention of the dye at 45 min.

7. *Serologic Tests.*—Mazzini tests were performed by Miss Nina Ferber, Maimonides Hospital, on the entire class at the zero- and four-month intervals.

RESULTS

Although a few of the students missed several days of school because of illness, the great majority were able to carry on, despite mild symptoms such as fatigability, malaise, headache, and sore throat. The main positive findings on physical examination were pharyngitis and moderate cervical adenopathy, especially of the posterior chain and the posterior occipital and auricular nodes—the last being the commonest nodes to be enlarged in infectious mononucleosis. Because of the relative mildness of these manifestations, evaluation of their significance would have been exceedingly difficult without supportive laboratory findings.

9. Davidsohn, I.: Test for Infectious Mononucleosis, Am. J. Clin. Path. (Tech. Supp.) **2**:56, 1938.

10. Dr. Annis E. Thomson, of the New York City Department of Health, furnished the antigens for our tests.

11. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, Ann. Int. Med. **21**:230, 1944.

12. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Invest. **18**:261, 1939. Neefe, J. R., and Reinhold, J. G.: Photosensitivity as a Cause of Falsely Positive Cephalin-Cholesterol Flocculation Tests, Science **100**:83, 1944.

13. Shank, R. E., and Hoagland, C. L.: A Modified Method for the Quantitative Determination of the Thymol Turbidity Reaction of Serum, J. Biol. Chem. **162**:133, 1946.

Since approximately 2,000 separate laboratory data were collected in the course of this study, it is obviously not possible to tabulate all of them here. Therefore,

TABLE 1.—*Data on Fifty-One Cases (of One Hundred Two) with Three or More Positive Findings for Infectious Mononucleosis at Some Time in Study**

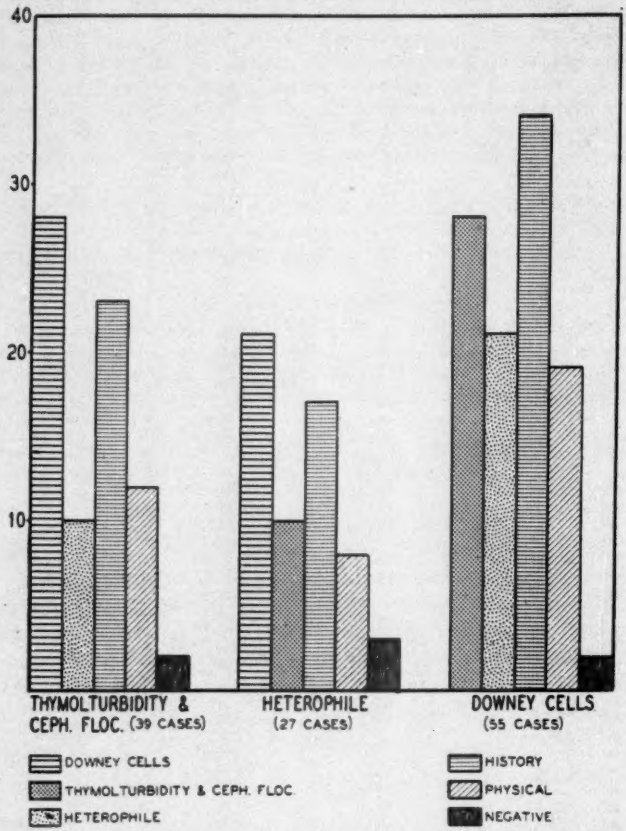
Case No.	History	Physical Signs	Thymol Turbidity, Units	Cephalin Flocculation	Absorbed Heterophile Titer	Downey Cells, %	Monocytes, %	Eosinophils, %
1	+	..	...	...	28	6	12	..
3	+	+	...	...	28	10	11	5
4	..	+	...	...	28	8	10	7
5	+	+	...	...	896	17	13	6
6	+	+	6.1	...	56	6	..	..
8	+	+	6.8	...	28	14	10	6
9	+	+	5.8	...	14	3	12	11
12	+	+	...	...	14	3	17	..
16	+	..	6.7	2+	28	..	..	..
25	+	..	6.7	...	14	9	..	8
27	+	..	...	2+	..	8	12	..
28	+	+	...	...	56	17	10	..
29	..	..	9.4	...	..	7	..	5
30	+	+	...	...	28	5	..	..
33	+	..	...	...	14	7	11	5
36	+	+	...	...	28	5	..	7
38	+	+	15.2	3+	..	14	16	..
44	+	..	...	...	..	4	16	14
48	+	..	...	...	28	4	..	..
50	+	+	5.0	3+	14	..	..	..
51	+	..	20.8	...	56	..	10	16
53	..	..	...	...	56	..	..	..
55	+	..	9.0	...	..	5	14	..
57	..	..	5.4	...	28	11	14	..
58	+	..	...	...	28	12	11	..
60	..	..	7.8	...	..	6	..	7
61	+	..	...	...	14	10	..	5
62	+	..	7.8	...	14	10	..	..
63	..	..	8.1	...	56	16	..	5
64	..	..	6.6	2+	28	5	13	5
67	..	..	...	...	28	11	11	..
70	+	..	6.8	...	56	14	..	5
71	+	..	6.0	2+	..	6	17	5
75	..	+	...	...	28	11	..	..
77	+	..	...	...	..	35	..	6
79	+	..	...	2+	..	5	11	..
80	+	..	...	...	14	8	..	..
81	+	..	...	...	28	9	..	..
82	..	..	8.6	...	14	7	..	..
83	+	+	5.0	2+	..	..	..	..
88	..	+	...	...	14	6	..	..
89	+	..	...	...	28	..	..	..
90	+	..	...	...	28	..	..	..
91	+	..	...	...	56	3	..	..
92	+	..	7.0	2+	56	10	..	..
94	+	+	8.8	3+	14	5	13	..
95	..	..	...	3+	14	6	11	..
97	+	..	...	...	28	..	..	..
98	..	...	16.2	..	..	10	..	10
100	+	..	...	...	14	10	..	7
102	+	+	6.4	2+	14	3	..	7

* Only the single highest abnormal value is given.

only the most interesting items will be listed. In Table 1 are presented the 51 cases in which there were three or more positive laboratory findings at any time in the survey, the maximally abnormal figure being listed. These 51 cases were thought to be infectious mononucleosis. In the Figure there is a group arrangement show-

ing correlation of other findings with the presence of Downey cells, abnormal flocculation reactions, and positive heterophile titers. It is apparent that there was a good degree of correlation with other abnormal findings.

Although only four students had positive absorbed heterophile titers of 1 : 28 or more at the initial bleeding, 27 displayed positive titers at the three-week period, the highest titer being 1 : 896. At the four-month period the titers of all except four of



Group arrangement showing correlation of positive reactions for infectious mononucleosis among 102 medical students.

the 27 had returned to normal, and, since the highest at that time was only 1 : 56, no further follow-up studies were done. An additional 28 students had titers of 1 : 14 at some time during the study.

The presence of Downey cells seemed to be the most sensitive test, since 55 of the 102 students had 3% or more some time during the investigation. Like the heterophile titers, these cells reached their highest peak at the three-week period.

Initially, 25 students had an increase in Downey cells; at three weeks, 35; at four months, 22; at six months, 12, and at 12 mo., only three students.

Of the 51 students thought to have infectious mononucleosis, 29 had a monocytosis (10% or more) and an eosinophilia (5% or more) at some time (see Table 2). The peak occurrence was at the fourth month, which then appears to be during convalescence. At 12 mo. these abnormalities had disappeared, so that only one student at this time was found to have eosinophilia (8%), and this person had had the highest number of Downey cells at the beginning. All students were ques-

TABLE 2.—*Monocytosis and Eosinophilia in Twenty-Nine of Fifty-One Cases of Infectious Mononucleosis**

Case No.	0		3 Wk.		4 Mo.		6 Mo.		12 Mo.	
	M, %	E, %	M, %	E, %	M, %	E, %	M, %	E, %	M, %	E, %
1	12	..	16	..	..	..	..	..	..	..
3	..	5	..	..	..	..	..	..	..	..
4	..	..	..	..	10	7	..	..	..	..
5	..	6	..	..	12	..	..	..	..	..
8	..	..	10	..	..	..	..	6	..	..
9	..	..	..	..	12	11	..	..	..	..
12	..	..	17	..	..	..	..	..	..	..
25	..	..	..	..	..	8	..	..	..	..
27	..	..	..	..	12	..	..	..	..	..
28	..	..	..	..	10	..	..	..	..	..
29	..	..	..	5	..	..	..	..	..	..
33	..	..	11	5	..	..	..	..	..	..
36	..	..	..	..	..	..	..	7	..	..
38	..	..	..	..	10	..	..	..	..	..
44	..	..	..	14	6	16	..	..	..	..
55	..	..	..	..	..	..	13	..	..	..
57	..	..	..	..	14	..	11	..	..	..
58	11	..	..	..	..	..	..	..	..	..
63	..	..	..	..	..	5	..	..	..	..
64	..	..	..	..	..	5	13	..	..	..
70	..	5	..	..	..	..	..	..	..	..
71	..	..	..	5	17	..	..	..	..	..
77	..	5	..	..	..	..	..	..	..	6
79	..	..	..	..	11	..	..	..	..	..
94	..	..	10	..	13	..	..	..	..	..
95	..	..	..	..	11	..	..	..	..	..
98	..	9	..	10	..	6	..	..	..	..
100	..	..	..	..	..	7	..	..	..	..
102	..	..	..	7	..	..	..	..	..	..
Total 29	2	5	5	6	12	8	3	2	..	1

* Only monocyte (M) values of 10% or more and eosinophil (E) values of 5% or more are listed.

tioned about a history of allergy. There were only four (Cases 1, 36, 63, and 94) in this group with a positive history.

Thirty-three of the 102 students had an elevated thymol turbidity of 5 units or more and 15 had cephalin-flocculation reactions of 2+ or more (see Table 3). In contrast to the peak incidence of Downey cells and positive heterophile titers at three weeks, the peak incidence here was at four months, coinciding with the height of the monocytosis and eosinophilia. At four months only one student (Case 38) of 33 with abnormal flocculation reactions had sulfobromophthalein dye retention at 45 min., and this was only 5%. At 12 mo. there were still seven students who had elevated thymol-turbidity values. This was in contrast to three students with persistent Downey cells and one with eosinophilia at this 12-mo. period. At 22 mo.

seven students had positive thymol-turbidity reactions, two of them also having strongly positive cephalin-flocculation reactions. At this time the serum bilirubin, cholesterol, albumin, and globulin were within normal limits.

None of the 51 students with positive findings for infectious mononucleosis had positive Mazzini reactions.

TABLE 3.—*Data on Cases with Abnormal Thymol-Turbidity and Cephalin-Flocculation Values**

Case No.	0		2 Wk.		4 Mo.		6 Mo.		9 Mo.		12 Mo.		22 Mo.	
	TT	CF	TT	CF	TT	CF	TT	CF	TT	CF	TT	CF	TT	CF
4	5.6	...	...	...	...	...	...	...	...	...	...	...	...	...
6	...	...	6.1	...	5.0	...	...	...	...	...	...	...	...	...
7	...	...	...	...	5.2	...	...	...	...	...	...	...	...	...
8	6.0	...	...	...	5.2	...	6.8	...	...	...	...	...	...	...
9	5.8	...	...	...	...	...	...	...	...	...	...	...	...	...
11	...	...	...	...	5.4	...	...	...	...	...	...	...	...	...
15	...	...	...	...	6.0	...	...	...	...	...	...	...	...	...
16	...	...	...	...	...	2+	6.7	...	5.6	...	...	...	...	...
24	...	...	...	...	...	3+	...	...	...	...	...	...	...	...
25	...	...	6.7	...	...	...	...	...	...	...	...	...	...	...
27	...	...	...	...	...	2+	...	...	...	...	...	...	...	...
29	...	...	5.7	...	5.4	...	6.9	...	...	...	...	...	9.4	...
38	7.0	2+	6.5	3+	...	...	15.2	...	5.8	...	5.5	...	12.2	3+
50	5.0	...	...	3+	...	...	...	...	...	...	...	...	...	...
51	10.7	...	9.8	...	12.0	...	8.3	...	20.8	...	...	...	16.6	...
55	...	...	7.0	...	5.4	...	6.2	...	6.2	...	5.0	...	...	...
56	...	...	6.2	...	6.5	...	5.4	...	...	...	...	...	...	...
57	...	...	5.4	...	...	...	...	...	...	...	...	...	...	...
59	...	...	5.0	...	...	...	...	...	...	...	...	...	...	...
60	...	...	5.5	...	7.8	...	7.0	...	6.4	...	...	...	...	...
62	...	...	7.0	...	7.8	...	6.0	...	...	...	5.2	...	9.0	...
63	5.5	...	8.1	...	5.6	...	5.0	...	...	...	5.4	...	...	4+
64	...	...	6.6	2+	6.5	...	5.2	...	...	...	...	...	...	...
66	5.0	...	...	...	...	...	...	...	...	...	...	...	...	...
70	...	...	...	...	6.8	...	5.0	...	...	...	5.2	...	5.8	...
71	...	...	...	...	6.0	2+	...	...	...	...	...	...	...	...
74	...	...	...	...	6.5	...	...	...	...	...	...	...	...	...
79	...	...	...	2+	...	...	...	...	...	...	...	...	...	...
82	...	...	...	...	8.6	...	8.0	...	7.2	...	5.2	...	5.7	...
83	...	...	...	2+	5.0	...	...	...	...	...	...	...	...	...
87	6.8	...	...	...	...	...	...	...	...	...	...	...	...	...
92	5.4	...	...	...	...	2+	7.0	...	...	...	...	...	...	...
94	8.4	...	...	...	8.8	2+	...	...	...	...	...	...	...	...
95	...	...	...	...	...	3+	...	...	...	...	...	...	...	...
98	11.2	...	11.3	...	9.4	...	16.2	...	...	...	12.8	...	9.8	...
99	...	...	...	3+	...	...	...	...	...	...	...	...	...	...
101	...	...	...	2+	...	...	...	...	...	...	...	...	...	...
102	...	...	...	...	...	2+	...	...	...	...	...	...	...	...
Total 38	12	1	14	7	20	8	15	..	6	..	7	..	7	2

* Only thymol-turbidity (TT) values of 5 units or more and cephalin-flocculation (CF) values of 2+ or more are listed.

COMMENT

If two of the three tests (presence of Downey cells, heterophile-antibody titer, and flocculation tests) had positive reactions, the disease was tentatively diagnosed as infectious mononucleosis. According to this criterion, 51 of the 102 students were thought to have the disease (Table 1). It is realized that this is somewhat arbitrary. In most instances a positive absorbed heterophile titer of 1:28 or more is considered highly indicative of infectious mononucleosis; 27 of our patients had

a positive titer, and 28 others had a titer of 1:14, which is considered by some authorities as highly suggestive.[11] The incidence of positive heterophile titers in clinical infectious mononucleosis is usually cited as 90%.[14] However, many agree that in the presence of other supporting laboratory and clinical data the diagnosis does not depend solely on the presence of the positive heterophile titer.

Infectious hepatitis seemed unlikely because there were no clinical cases of jaundice at the time and because a positive heterophile titer is used as the main means of differentiating the two diseases.[15] Atypical virus pneumonitis, another disease which can cause atypical lymphocytes, does not give a positive heterophile reaction. Furthermore, cough was not a clinical feature of our cases. "Grippe" or epidemic influenza is not known to cause a high incidence of positive cephalin flocculation,[16] elevated thymol turbidity, or positive heterophile reactions.[11]

Although it is possible that a few of these 51 students might not have had infectious mononucleosis, it is also likely that if complete studies had been done on every student once a week for four to eight weeks during the height of the epidemic several other students might have been found to have significantly positive reactions. Since they did not all contract the illness simultaneously, laboratory tests would have been expected to show abnormalities at different times. Furthermore, the evanescence of these reactions is well known.

It appears that Downey cells were the most sensitive indicator of the disease, since 55 of the 102 students were found to have increases, and 43 of these 55 had two or more other abnormal laboratory findings. The fact that 12 of these students still showed Downey cells at six months is not surprising, since it is well known that they may persist for long periods.

Monocytosis has been described [8] in the convalescent stage of the disease and eosinophilia in the acute as well as in the convalescent stage.[17] In our series 11 students showed eosinophilia in the first three weeks, and 10 at the four- and six-month periods. Seven showed monocytosis in the first three weeks and 15 at the four- and six-month periods. The eosinophilia seemed fairly uniformly distributed as to time, while the monocytosis seemed more prominent with convalescence, at which time the Downey cells were subsiding.

Although a false-positive Wassermann or Mazzini reaction is not uncommon in infectious mononucleosis, none of our 51 students with other reactions to laboratory tests indicative of infectious mononucleosis had positive Mazzini reactions.

One of the greatest surprises was the high number of abnormal thymol-turbidity and cephalin-flocculation reactions in these subclinical cases and their persistence for long periods. Thirty-nine students showed these abnormalities, which persisted in seven at the 12-mo. period and in seven at the 22-mo. period. Although the presence of hepatitis in 70 to 90% of cases of clinical infectious mononucleosis without jaundice has been emphasized in recent years,[18] the presence of hepatitis in sub-

14. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1946.

15. Berk, J. E.; Shay, H.; Ritter, J. A., and Siplet, H.: Infectious Mononucleosis and Infectious Hepatitis: Studies Bearing on Certain Resemblances and Differences, Gastroenterology **11**:658, 1948.

16. Evans, A. J.: Liver Involvement in Infectious Mononucleosis, J. Clin. Invest. **27**:106, 1948.

17. Kaufman, R. E.: Eosinophilia in Infectious Mononucleosis, Am. J. M. Sc. **219**:206, 1950.

18. Footnote 6. Evans.[16]

clinical cases such as ours has not been previously studied. Since there was only one slightly positive sulfobromophthalein reaction, the hepatitis in our cases was undoubtedly mild. Unfortunately, sulfobromophthalein tests were not done until the fourth month, some time after the peak of the epidemic. It is possible that if the test had been performed earlier more positive reactions would have been found. Since changes in the serum proteins in infectious mononucleosis were found in all of seven cases by Sterling,[19] using electrophoretic methods, it is possible that the abnormal cephalin-flocculation and thymol-turbidity reactions may be dependent upon these protein abnormalities and may be nonspecific reactions rather than reactions dependent upon liver dysfunction. This seems relatively unlikely, however. A recent report [7] of a case of cirrhosis of the liver following infectious mononucleosis emphasizes the importance of long-term follow-up studies of many cases of infectious mononucleosis.

It is evident, then, that there probably was an organic basis for high incidence of weakness, fatigue, and malaise which seemed severer than the usual "spring fever" in our second-year medical students in the sping of 1949. Contratto [20] has stated that continuous complaints of fatigue and malaise associated with no abnormal physical findings may lead to a diagnosis of neurosis until the blood is examined. It may be that hepatitis is the main cause of such symptoms.

SUMMARY

A class of 102 "normal" medical students was studied during an epidemic of clinical infectious mononucleosis. Laboratory studies were done at intervals for 22 mo. Fifty-one students showed laboratory evidence of infectious mononucleosis, although the disease was largely subclinical. Thirty-five students showed monocytosis, eosinophilia, or both. Thirty-three students showed a positive thymol-turbidity reaction, in seven of whom the reaction was still positive 22 mo. later.

The high incidence of hepatitis in subclinical cases of infectious mononucleosis deserves special attention.

Dr. Jacqueline Messite and Dr. John Meyer assisted us in the collection of data.

19. Sterling, K.: The Serum Proteins in Infectious Mononucleosis: Electrophoretic Studies, J. Clin. Invest. **28**:1057, 1949.

20. Contratto, A. W.: Infectious Mononucleosis: A Study of 196 Cases, Arch. Int. Med. **73**:449 (June) 1944.

THE ADRENAL CORTEX IN RHEUMATIC DISEASE

Pathologic Study with Special Reference to Effects of Cortisone and Corticotropin

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THE RESPONSE of certain rheumatic diseases to the administration of cortisone and the adrenal corticotropic hormone of the anterior lobe of the pituitary (corticotropin; ACTH) has aroused an interest in structural changes of the adrenal cortex in these diseases. The present study is a systematic investigation of the human adrenal cortex in persons with several rheumatic conditions and in persons receiving cortisone or corticotropin therapy. Although there are numerous well-controlled observations of the morphological variations of the adrenal cortex of laboratory animals in different physiological conditions, relatively little information is available concerning the human gland in systemic diseases. There is a fairly wide variation in the weight, size, and microscopic appearance of the cells that has not been clearly correlated with the general state except in obvious conditions of hypoadrenalism (Addison's disease) or of hyperadrenalism, as in certain cases of Cushing's syndrome. In addition to a careful histological examination of the adrenal glands, three types of measurements have been made in the present study:

1. The combined weights of the adrenal glands have been determined as an index of hypertrophy and atrophy.

2. The cholesterol content of the glands has been determined. Cholesterol constitutes the bulk of the steroid of the cortex [1] and may be the precursor of the steroid hormones.[2] The cholesterol and other lipids are contained within the cytoplasm of the cortical cells. In histological sections that have been treated with fat solvents, the lipid content of the cells is indicated by the degree of cytoplasmic vacuolation. For this reason, variations in the lipid content are responsible for many of the different appearances of the cells.

3. A quantitative analysis of the zonal architecture of the cortex has been made. This was undertaken for three reasons: Firstly, it provides a tool for histological comparison of different glands. Secondly, as will be demonstrated presently, the

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From the Departments of Pathology, New York University College of Medicine and Bellevue Hospital, and the Study Group on Rheumatic Diseases.

1. Adams, E., and Baxter, M.: Lipid Fractions of Human Adrenal Glands, Arch. Path. 48:13 (July) 1949.

2. Sayers, G.: Adrenal Cortex and Homeostasis, Physiol. Rev. 30:241, 1950.

measured thickness is a fairly accurate index of the weight of the adrenal gland, when the weights are not known. This has been important because it has not proved possible to obtain control materials from untreated patients with rheumatic diseases since the advent of hormonal therapy. Thirdly, within recent years, a number of investigators have suggested, on the basis of experiments with laboratory animals, that the various histological zones of the adrenal cortex have independent secretory functions [3] and different integrations with the anterior lobe of the pituitary.[4] Sayers has called this theory the "autonomy concept" of the nature of the adrenal cortical steroid secretion,[2] referring to the autonomy of the zones.

METHODS AND MATERIALS

The fibroadipose tissue surrounding the fresh organs was dissected away from the capsule as carefully as possible with sharp scissors. Because of conditions beyond our control, it was not possible to obtain all the glands as soon after death as might be desired. Nevertheless, except in a few instances, they were removed within the first 24 hours. The cholesterol and lipid are generally fairly resistant to autolytic change. The glands were weighed to the nearest 50 mg., except for several in the cases first studied that were weighed to the nearest 100 mg. The outlines of the glands were traced. Blocks were taken from the entire width of the transverse midportion of the organs. They were fixed in 4% formaldehyde solution (formalin®) and in Zenker's solution (a fixative solution of corrosive mercuric chloride, potassium bichromate, and water) without the addition of acetic acid.

The remainder of the adrenal glands was weighed, minced with scissors, and dried in a high-vacuum pump over anhydrous calcium chloride. The weight of the desiccated glands was determined, and the wet-to-dry ratio calculated. An aliquot of 100 mg. was extracted with chloroform for three hours in a Soxhlet apparatus. The extract was made up to a volume of 100 ml. A Bloor-type colorimetric determination of cholesterol was then made on the undiluted extract and on the extract diluted 1:1 with chloroform. The colors were compared with that of one of three standard solutions of cholesterol (2 mg., 1 mg., and 0.4 mg. per milliliter) in a Duboscq colorimeter. Although we are well aware of the limits of this method of analysis, the control values correspond well to those obtained with more exacting methods.[1]

Frozen sections were made from comparable blocks taken through the width of the midportion of the glands. These were stained with scarlet red (Sudan IV). The sections were projected at a magnification of 51 diameters; tracings were made of the cortex and its zones. The thickness of the zones was measured at 30 to 50 points (usually at 40) in each case. The results have been expressed as average thickness in millimeters. The limits of the zones are not sharply defined and may be differently interpreted by different persons. To ensure as consistent an interpretation as possible, all the tracings were made by one observer. The anatomic pattern

3. Deane, H. W.; Shaw, J. H., and Greep, R. O.: The Effect of Altered Sodium or Potassium Intake on the Width and Cytochemistry of the Zona Glomerulosa of the Rat's Adrenal Cortex, Endocrinology **43**:133, 1948. Nichols, J.: Effects of Electrolyte Imbalance on the Adrenal Cortex, Arch. Path. **45**:717 (June) 1948.

4. (*a*) Yoffey, J. M., and Baxter, J. S.: Histochemical Changes in the Suprarenal Gland of the Adult Male Rat, J. Anat. **83**:89, 1949. (*b*) Bergner, G. E., and Deane, H. W.: Effects of Pituitary Adrenocorticotropic Hormone on the Intact Rat, with Special Reference to Cytochemical Changes in the Adrenal Cortex, Endocrinology **43**:240, 1948. (*c*) Miller, R. A.: Cytological Phenomena Associated with Experimental Alterations of Secretory Activity in the Adrenal Cortex of Mice, Am. J. Anat. **86**:405, 1950. (*d*) Jones, I. C.: The Effect of Hypophysectomy on the Adrenal Cortex of the Immature Mouse, ibid. **86**:371, 1950. (*e*) Deane, H. W., and Greep, R. O.: Morphological and Histochemical Study of the Rat's Adrenal Cortex After Hypophysectomy, with Comments on the Liver, ibid. **79**:117, 1946. (*f*) Selye, H., and Stone, H.: On the Experimental Morphology of the Adrenal Cortex, Springfield, Ill., Charles C Thomas, Publisher, 1950.

of the zones illustrated by Goormaghtigh has been followed [5] rather than that shown by Maximow and Bloom [6] (Fig. 1). According to Goormaghtigh, the zona reticularis comprises the innermost cords of cells that are oriented principally in the plane parallel to the surface of the gland. The bulk of the human cortex consists of zona fasciculata. Whether or not the above concept is valid, it was followed because it was not possible to determine the exact point of transition between the fasicular and the reticular zones, as understood by Maximow and Bloom, in partly autolyzed human material. In regions where small areas of adenomatoid nodularity were encountered, the measurement was omitted. In a small proportion of the cases, this change was so marked that no estimate of the zonal thicknesses was warranted. Frozen sections were selected for this study rather than paraffin-embedded ones because freezing avoids the shrinkage that occurs with the paraffin technique. Furthermore, the configuration of the cords and nests of cells is frequently less distorted, since the cells are less easily detached from their basement membranes in the frozen preparations.

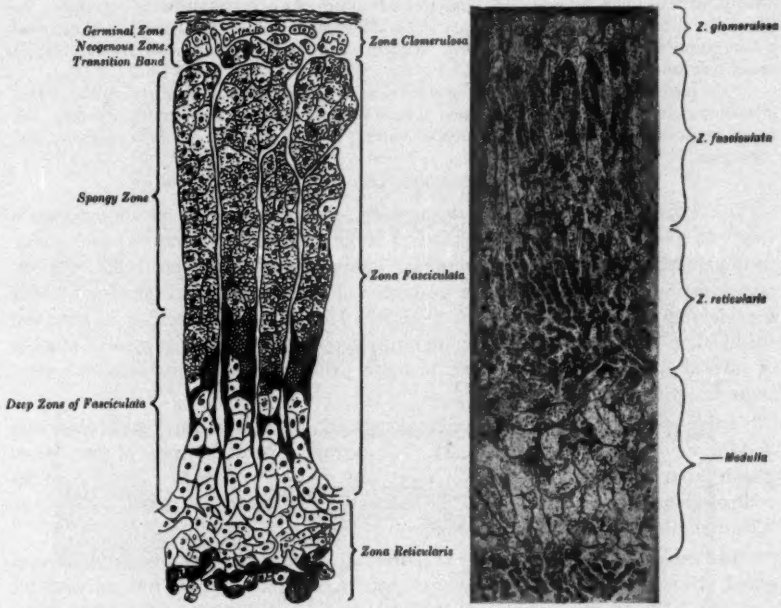

Fig. 1.—Left, schematic representation of zones of human adrenal cortex, according to Goormaghtigh. Reproduced, with permission, from Soffer, L. J.: Diseases of the Adrenals, ed. 2, Philadelphia, Lea & Febiger, 1948, p. 18, Fig. 2. Right, section of an adrenal gland of a man, showing zones of human adrenal cortex, according to Maximow and Bloom. Mallory-azan stain; reduced from a magnification of about × 105. Reproduced, with permission, from Maximow and Bloom,[6] p. 319, Fig. 269.

One hundred twenty-six glands from persons who died of various causes have been studied by these methods. These include 12 apparently healthy adults who died of trauma; in most instances, death was sudden, but in a few, the person survived the injury up to half an hour. Similar observations were made on three healthy children who died of trauma. For controls

5. Goormaghtigh, N.: Le cortex surrénal humain dans les plaies de l'abdomen et aux périodes intéressantes de la vie sexuelle, Thesis, Liége, 1922.

6. Maximow, A. A., and Bloom, H.: A Textbook of Histology, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

in various pathologic states, glands were obtained from 65 adults who died of a wide variety of diseases without obvious endocrine dysfunction and without treatment with hormonal preparations. Adrenal glands were available from three persons with large tumors that apparently destroyed the anterior lobe of the pituitary. These consisted of a chromophobe adenoma, a craniopharyngioma, and a degranulated eosinophilic adenoma in a patient with acromegaly. The adrenal glands from 33 persons to whom varying doses of corticotropin or cortisone were administered have been examined. These include five patients with active rheumatoid arthritis, five with rheumatic carditis, four with disseminated lupus erythematosus, and the remainder with miscellaneous conditions.

Since it was not possible to acquire adrenal glands from persons having rheumatic disease that had not been treated with either of these preparations, it was necessary to utilize stored material from necropsies performed in the past. In this way, adrenal glands of eight adults and four children with active rheumatic carditis, four adults with rheumatoid arthritis, and isolated patients with disseminated lupus erythematosus were made available for study. In addition to the information concerning size and architecture that might be obtained from sections, a fair estimate of the cholesterol content could be made from the amount of sudanophilic or anisotropic substance [7] in the cortex.

In the microscopic examination of the cortical cells, special attention was paid to the degree of adenomatoid nodularity, the distribution of lipid in the cortex, and degenerative changes. The latter included formation of pseudotubular lumens, colloid droplets in the cytoplasm, and "cytolysis." [4f]

RESULTS

In the group of healthy adults, the average combined weight of the adrenal glands was 9.35 gm., the range being 6.10 to 13.50 gm. These values correspond closely to those reported for much larger series.[8] Among the adults who died of various nonendocrine diseases, there were a number of persons who had glands weighing considerably more; the heaviest of these was 18.4 gm., the lightest, 6.30 gm., and the average, 11.0 gm. In the older literature reports are found that a small number of adrenal glands may weigh 20 gm. or more, principally in association with severe, acute infections.[9]

There was an approximately linear correlation of the average cortical thickness and the weight of the glands (Fig. 2). The average cortical thickness of the adrenal glands from healthy adults was 1.21 mm., with a range of 0.86 to 1.76 mm. In the control glands from patients who died of various diseases, the range was 0.85 to 2.16 mm., the average being 1.30 mm.

The cholesterol content has been reported as percentage of wet weight of adrenal gland. In healthy adults this value was quite high, although there was considerable variation. The average figure was 9.6 gm. per 100 ml., ranging from a low of 4.7 to a high of 14.9 gm. per 100 ml. In disease, this diminished to a variable extent. In conditions associated with sudden death, e. g., in some instances of myocardial infarction, the amount of cholesterol was great; nevertheless, it was occasionally as abundant in diseases of longer standing. In cases of hypertension, the depletion of cholesterol was, in general, somewhat less marked than in other conditions. This

7. Sayers.[2] Rogers, W. F., Jr., and Williams, R. H.: Correlations of Biochemical and Histologic Changes in Adrenal Cortex, Arch. Path. **44**:126 (Aug.) 1947.

8. (*a*) Materna, A.: Neue Untersuchungen über das Gewicht der Nebennieren, Beitr. path. Anat. **106**:158, 1942. (*b*) Quinan, C., and Berger, A. A.: Observations on Human Adrenals, with Especial Reference to the Relative Weight of the Normal Medulla, Ann. Int. Med. **6**:1180, 1933.

9. Materna.[8a] Sarason, E. L.: Adrenal Cortex in Systemic Disease: A Morphologic Study, Arch. Int. Med. **71**:702 (May) 1943.

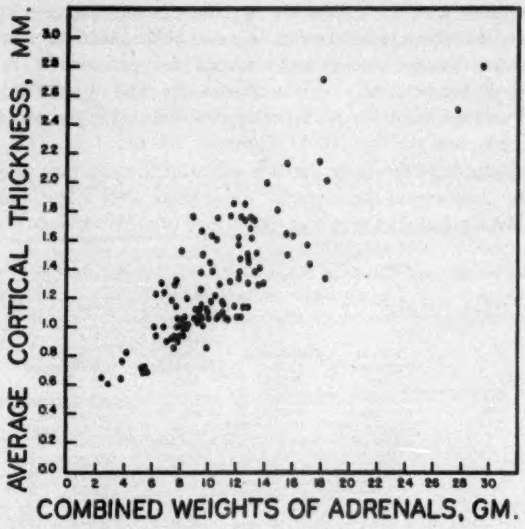

Fig. 2.—Relation of average thickness of the human adrenal cortex to weight of pair of adrenal glands.

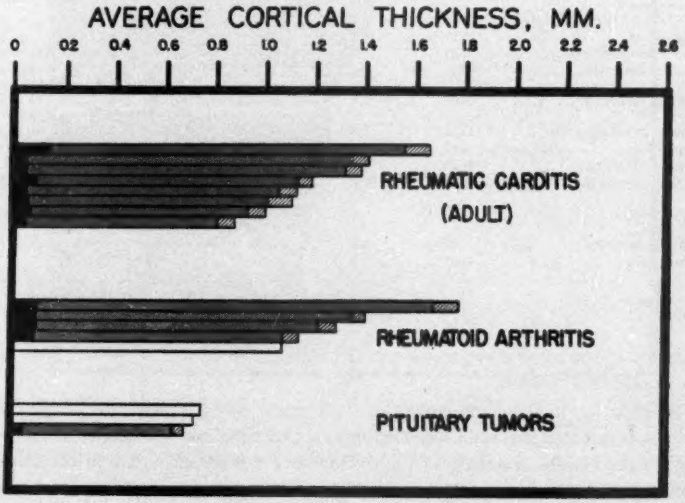

Fig. 3.—Analysis of zonal architecture of adrenal glands of group of adults with rheumatic carditis and with rheumatoid arthritis, not treated with cortisone or corticotropin. Third group consists of adrenal glands of three persons with large tumors causing destruction of anterior lobe of pituitary gland.

observation coincides with the experience of a number of observers [1] but does not support the view that there is an absolute increase of the cholesterol content in this disease.[10] In certain instances there was a virtual disappearance of the cholesterol, although this could not be clearly correlated with any type of systemic lesion or its duration. The average value for all types of illness was 5.0 gm. per 100 ml.; the lowest was 0.5 gm., and the highest, 11.3 gm. per 100 ml.

The adrenal glands of the three patients who had the pituitary tumors weighed considerably less than any of the controls; the weights were 5.4, 5.4, and 5.55 gm., respectively. The cortical thickness was diminished to a corresponding degree (Fig.

Summary of Data on Adrenal Glands of Nineteen Patients Treated with at Least One Gram of Cortisone or Corticotropin

Diagnosis	Weight Combined, Gm.	Cholesterol, % Wet Weight	Average Cortical Thickness, Mm.	Medicament, Mg.	Time Medication Discontinued
Normal adults (12): traumatic death	9.35* 6.10-13.50†	9.6* 4.7-14.9†	1.21* 0.80-1.76†	....	....
Adults (65): various diseases	11.0* 6.40-18.40†	5.0* 0.5-11.3†	1.30* 0.85-2.16†	....	....
Rheumatoid arthritis	29.40	1.2	2.79	Cortisone 3,600 ACTH 4,100	2 mo. .....
Third-degree burns	27.85	0.4	2.60	ACTH 4,810	.....
Infectious hepatitis; aspergillosis	14.25	3.9	2.00	ACTH 3,175	9 days
Disseminated lupus erythematosus	15.70	3.8	1.51	ACTH 10,290	5 wk.
Disseminated lupus erythematosus	8.35	0.2	1.08	ACTH 2,025	4½ mo.
Pulmonary fibrosis	8.95	3.3	1.51	ACTH 1,755	13 days
Status asthmaticus	5.50	6.0	0.72	Cortisone 6,100	.....
Rheumatic heart disease (13 yr.)	4.10	2.4	0.82	Cortisone 3,600	.....
Acute leukemia	12.90	4.7	1.27	Cortisone 5,200	.....
Rheumatic heart disease	12.65	2.3	1.04	Cortisone 3,900	32 days
Rheumatoid arthritis	9.35	2.6	1.07	ACTH 1,150 Cortisone 12,725	5½ mo. 2 mo.
Rheumatoid arthritis	16.00	0.6	1.63	ACTH 1,015 Cortisone 16,725	33 days 19 days
Pulmonary granulomatosis	11.10	1.8	1.15	Cortisone 4,700	40 days
Berylliosis	9.60	4.5	1.09	Cortisone 2,350	16 days
Myelogenous leukemia	11.35	4.3	1.06	Cortisone 2,200	5 mo.
Exfoliative dermatitis	6.35	0.3	0.94	ACTH 3,800 Cortisone 4,225	29 days 17 days
Ulcerative colitis	18.10	0.8	2.71	Cortisone 2,000 Cortisone 500	5 mo. .....
Rheumatoid arthritis	7.60	4.4	1.29	Cortisone 1,300	3 days
Acute leukemia	11.15	1.3	....	Cortisone 1,000	2 days

* Average.
† Range.

3). In two of the three there was a marked, and in the third a moderate, diminution of the cholesterol content.

The variation in the arrangement of the cortical zones is illustrated in Figure 4. It will be noted that different diseases induce little qualitative change in the architecture of the glands. Increase of the thickness of the cortex is due principally to a widening of the zona fasciculata, apparently resulting from an increase of the number of cells. The appearance of the glands in rheumatoid arthritis and in rheumatic carditis is not different from that in the nonrheumatic diseases (Fig. 3). The similar

10. Rogers, W. F., Jr., and Williams, R. H.: Cholesterol of the Human Adrenal Gland: Its Significance in Relation to Adrenal Function and Structure, Arch. Path. **46**:451 (Nov.) 1948.

average cortical thicknesses indicate that the glands are neither hypertrophied nor atrophied when compared with those from nonrheumatic persons. The degree of diminution of sudanophilic and of anisotropic material, presumably the cholesterol content, is neither consistent nor characteristic. There are no special changes in the appearance of the cells of these adrenal glands in the rheumatic diseases.

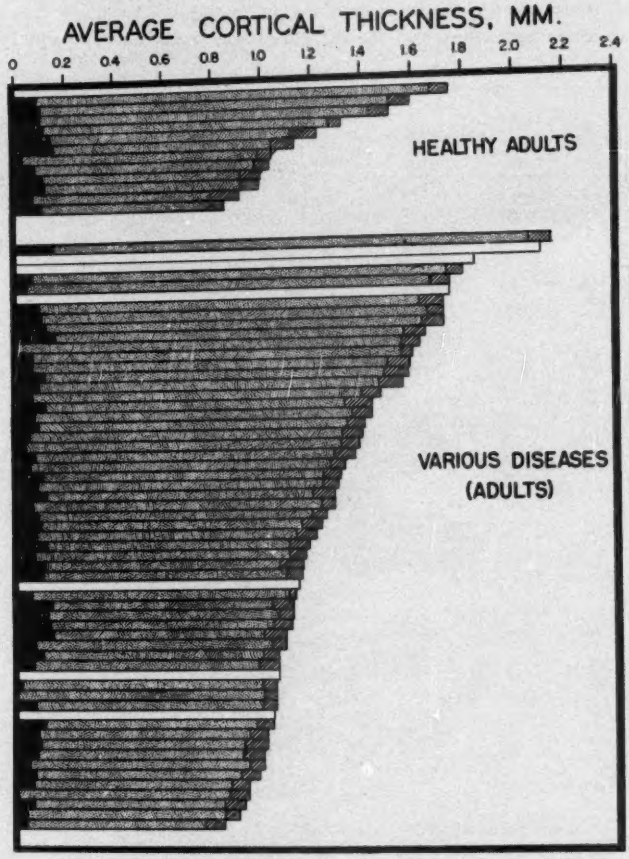

Fig. 4.—Analysis of zonal architecture of adrenal cortex of 12 healthy and 64 diseased adults. Zona glomerulosa is designated with oblique lines; zona fasciculata is intermediate and stippled; zona reticularis is at the left and black. Long white spaces without divisions indicate that zones could not be delimited because of nodularity or autolysis.

The data concerning the adrenal glands of 19 patients treated with at least 1 gm. of cortisone or corticotropin are summarized in the Table. With small doses of either preparation (2,000 mg. or less), distinctive changes were not observed. In the two persons who died while receiving corticotropin in large amounts, the paired glands weighed 27.85 and 28.4 gm., respectively. This increase of weight is highly significant statistically. There was a corresponding increase of the average cortical

thickness. The cortical cells were individually somewhat enlarged; the nuclei were frequently enlarged, and there was a true hyperplasia in addition. Most of the cells were arranged in fascicular cords. Nevertheless, the hypertrophy of the individual cells was not confined to any single layer. They were, for the most part, markedly depleted of cytoplasmic vacuoles and cholesterol. The cytoplasm was eosinophilic. In one of these two cases a considerable proportion of the cells, perhaps 10%, revealed degenerative changes, referred to as "cytolysis" by Selye [11] and others. These were somewhat swollen; the cytoplasm was water-clear, except for a few

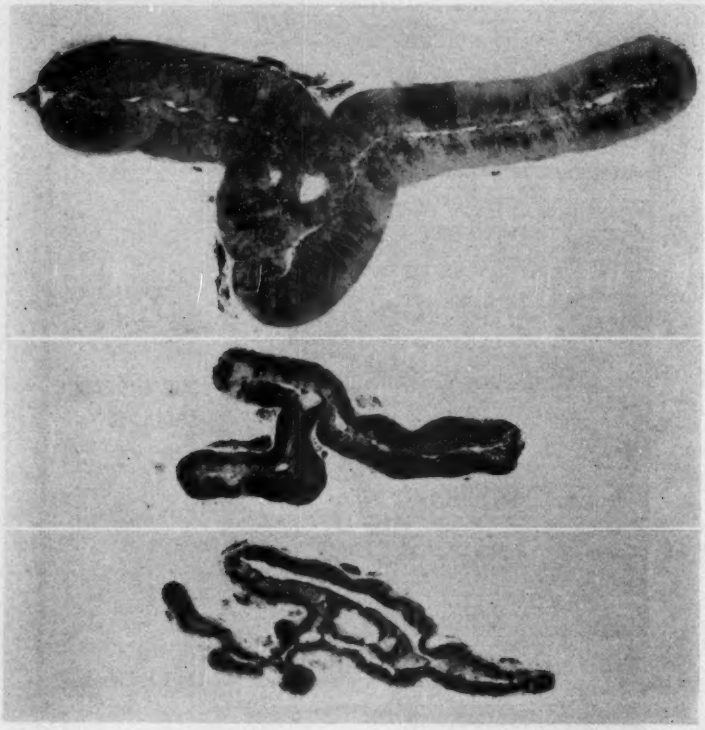

Fig. 5.—Cross sections of adrenal glands of healthy adult (center); of adult treated with large amounts of corticotropin (top), and of adult treated with large amounts of cortisone (bottom). Sudanophilic material appears black. Photographs were made at same magnification.

eosinophilic granules, but contained no lipid; the nuclei were shrunken and pyknotic. These changes were most marked in the innermost portions of the cortex, principally in the fascicular zone.

On the other hand, in the instances in which the administration of corticotropin had been discontinued for some time before the person died, the glands could not be distinguished from those of diseased persons who had not received this medicament. In one case the interval between cessation of therapy and death was only nine days.

In a person who had received massive quantities of cortisone in treatment of bronchial asthma there was a definite atrophy in terms of weight, cortical thickness, and the microscopic appearance of the cells. The degree of atrophy is similar

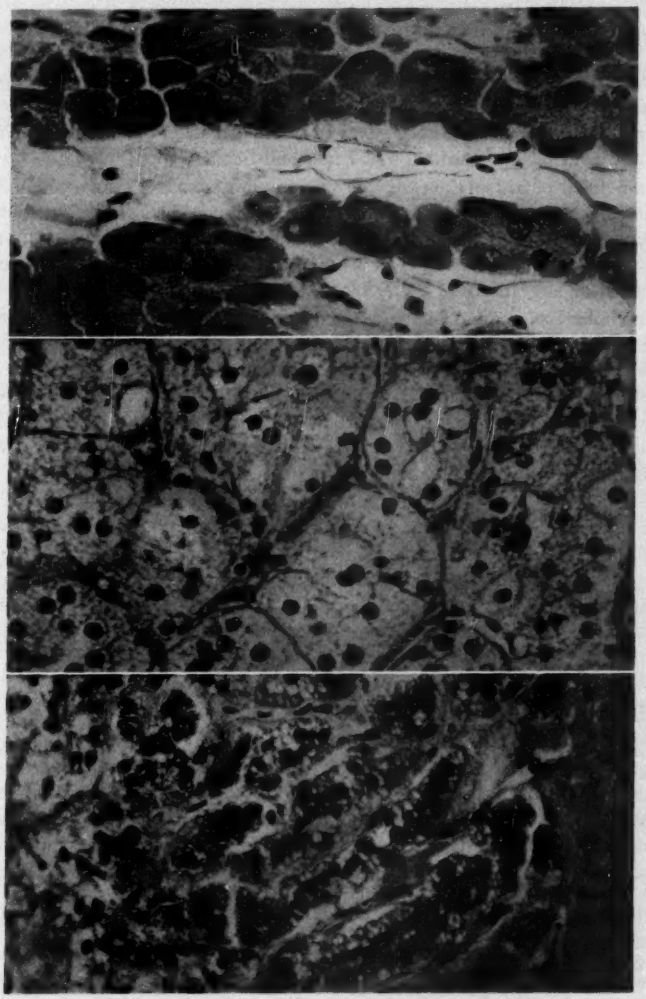

Fig. 6.—Microscopic appearance of outer cortical cells of healthy adult (center); of an adult treated with large amounts of corticotropin (top), and of adult treated with large amounts of cortisone (bottom). Photographs were made at same magnification (× 664).

to that observed in association with the pituitary tumors. Nevertheless, in the glands of another person who had received comparable quantities of cortisone, although over a shorter time, there was no atrophy. In the former, the cortisone

had been administered over a four-month period; in the latter, over 18 days. A 13-year-old girl, who had received 3,600 mg. of cortisone and to whom the drug was administered until the day of death, had small adrenal glands that may have been atrophic, though there are too few controls in this age group to prove it. According to the standards presented by Benner [11] and by Schilf,[12] these adrenal glands would be classified as atrophied. Nevertheless, their data are based largely upon adrenal glands obtained in conditions in which some hypertrophy might be expected. The few specimens we have studied from persons after traumatic death indicate that the normal adrenal gland in childhood may weigh considerably less than the weight given as normal by Benner and Schilf.

In a number of instances in which even enormous amounts of cortisone had been administered over many months, but in which treatment had been discontinued for some time before death, the adrenal glands had no distinctive changes. In one case this interval was only 19 days. Nor were unusual changes observed in the cortices when small or large doses of corticotropin and cortisone had been alternated.

The cholesterol content of the adrenal cortex from the two persons who were continuously treated with corticotropin until death approximately one month later was reduced to a great degree. This appeared to be an absolute as well as a relative diminution. In three of four persons to whom the administration of corticotropin was discontinued for a period as short as nine days before death, the cholesterol concentration in the glands apparently rose. The diminution of cholesterol was not striking in persons who died while receiving cortisone.

In no instance was the architecture of the cortex fundamentally altered by the hormonal medications. In the glands with the cortisone-induced atrophy, the diminution of the size of the cells occurred in all the zones; the same is true of the hypertrophy due to the administration of corticotropin. An unusual degree of adenomatoid nodularity was not consistently present. There was no alteration of reticular pigmentation, increase of basophilic material in the cytoplasm,[13] pseudotubular change,[14] or adipose metaplasia.[4f]

COMMENT

Although there admittedly are few structural variations of the adrenal cortex, when one considers the innumerable and sensitive functional responses of this organ to a host of stimuli it is apparent from the data presented here, as well as from laboratory experiments, that the adrenal cortex possesses a certain morphological lability. The amount of human material available for our study is quite small, and the interpretations offered here are only tentative. Only tentative interpretations are valid because there may be considerable variation in the potency of the prepa-

11. Benner, M. C.: Studies on the Involution of the Fetal Cortex of the Adrenal Glands, Am. J. Path. **16**:787, 1940.

12. Schilf, F.: Die quantitativen Beziehungen der Nebennieren zum übrigen Körper, Ztschr. Konstitutionslehre **8**:507, 1922.

13. Rich, A. R., and Berthrong, M.: Evidence for the Presence of Ribonucleic Acid in the Cytoplasmic Bodies That Appear in the Hepatic and Adrenal Epithelial Cells of Man in Acute Infection, Bull. Johns Hopkins Hosp. **85**:327, 1949.

14. Selye and Stone.[4f] Rich, A. R.: Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections and Its Possible Relation to Circulatory Collapse, Bull. Johns Hopkins Hosp. **74**:1, 1944. Golden, A.: Cortical Necrosis of Adrenal Gland in Man: Evolution and Varieties of Acute Necrosis and Its Repair, Am. J. Clin. Path. **19**:918, 1949.

rations, their absorption, and the reactivity of the tissue to them. Adrenal cortical hypertrophy and hyperplasia have resulted from stimulation by the adrenal corticotropic hormone of the pituitary in rats,[15] mice,[4c] guinea pigs,[16] rabbits,[17] and dogs.[17a] In some of these animals, at least, this response may be elicited promptly by the administration of a single dose of the preparation [18] and disappear soon thereafter. Characteristically, this initial response is associated with a depletion of the cholesterol content of the cortical cells. Nevertheless, in certain circumstances of protracted stimulation, it is believed by some that the cholesterol may remain relatively inert and, indeed, may sometimes increase greatly in the cortex.[10]

The result of the present investigation clearly demonstrates that a highly significant degree of cortical hyperplasia and hypertrophy occurs in the human organ as a result of the administration of corticotropin. In addition to the two cases presented here, similar observations have been reported in the literature.[19] Unlike the results obtained in the small laboratory animal, distinctive changes in the human adrenal gland are not observed as the result of administration of a single dose of corticotropin, or of repeated doses until a large total has been accumulated. When the medication is stopped, regression apparently occurs, so that one cannot distinguish these adrenal glands from those of persons who had not been treated with corticotropin. In the material available for our study, this reversal had apparently occurred within as short a time as nine days.

The protracted administration of various adrenal cortical hormonal preparations in large doses has repeatedly been reported to induce considerable atrophy of the adrenal cortex of laboratory animals. Presumably, this results from suppression of the secretion of the adrenal corticotropic hormone of the pituitary. Cortin accomplishes this in rats.[20] Cortisone does the same in rats,[21] mice,[22] rabbits,[23] and

15. (*a*) Footnote 4*a* and *b*. (*b*) Swann, H. G.: Pituitary-Adrenocortical Relationship, Physiol. Rev. **20**:493, 1940. (*c*) Ducommun, P., and Mach, R. S.: Effet de l'hormone adrénocorticotrope sur la morphologie du cortex surrénalien, son contenue en acide ascorbique et en esters de cholésterol chez le rat normal, Acta Endocrinol. **3**:17, 1949.

16. Hyman, G. A.; Ragan, C., and Turner, J. C.: Effect of Cortisone and Adrenocorticotropic Hormone (ACTH) on Experimental Scurvy in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **75**:470, 1950.

17. Germuth, F. G.; Nedzel, G. A.; Ottinger, B., and Oyama, J.: Anatomic and Histologic Changes in Rabbits with Experimental Hypersensitivity Treated with Compound E and ACTH, Proc. Soc. Exper. Biol. & Med. **76**:177, 1951.

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(Footnotes continued on next page)

chicks.[24] Atrophy has also been reported to follow the administration of other corticosteroids: desoxycorticosterone and compounds A and F. In the present study it is seen that a similar change may result from the administration of cortisone in man, though this change is not observed consistently. The degree of atrophy is comparable with that observed in the three instances of destruction of the pituitary gland by tumor. Although it would appear that large amounts of cortisone have to be given before atrophy results, other factors must be involved. Bennett [19d] has suggested that the duration of treatment is of greater importance than the dosage. The lack of atrophy in the glands of the person who had received 5,200 mg. of cortisone (Case 9) supports this view, since it had been administered for only 18 days.

On the other hand, it is clear that when this medication was discontinued, even after a long course of treatment, the glands were not atrophic. Nor did they have other distinctive histological abnormalities. It may be inferred that if atrophy had been present while the patient was receiving cortisone restoration of the glands to normal size occurred after cessation of treatment. Such a sequence of events is known to occur in the experimental animal.[21] This restitution apparently took place, in one instance, within 19 days. Review of the data presented from the Mayo Clinic,[25] and also of our own control material, confirms the impression that diminution of the adrenal mass is not seen commonly after the administration of cortisone, and certainly not after its use has been discontinued for some time. The massive "cytolysis" of the cortex reported by Proctor and Rawson [25a] 11 days following cessation of a course of cortisone and corticotropin therapy is apparently the only instance described so far. Combined courses of treatment with these preparations caused no lasting change in the series presented here. Nevertheless, there are clinical evidences that adrenal cortical function may be depressed for some time after the prolonged use of cortisone.[26]

No differences have been observed in the adrenal glands of patients with active rheumatic heart disease, rheumatoid arthritis, or disseminated lupus erythematosus that would distinguish them from those of persons with nonrheumatic diseases. The response to cortisone and corticotropin was the same as in those who did not have these diseases. These facts suggest that disturbances of the adrenal cortex are not of primary importance in the pathogenesis of rheumatic diseases.

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SUMMARY AND CONCLUSIONS

In addition to a careful histological examination of the adrenal gland, three types of measurement were made in the present study: (1) weight, (2) cholesterol content, and (3) a quantitative analysis of the zonal architecture. The adrenal cortex in rheumatic diseases shows no changes to distinguish it from the adrenal cortex in nonrheumatic diseases. Small doses (2,000 mg. or less) of corticotropin or cortisone do not cause appreciable change. Large doses of corticotropin induce marked hypertrophy that apparently regresses after cessation of therapy. Large doses of cortisone sometimes result in atrophy. The cortex is restored to normal size when the medication is discontinued. The adrenal cortex in rheumatic diseases responds in the same manner to corticotropin and cortisone treatment as it does in nonrheumatic diseases. Permanent morphological alteration does not commonly result from the administration of these preparations.

The following persons permitted use of their material: Dr. Milton Helpern, Dr. Henry Weinberg, and Dr. Robert Fisher, of the Chief Medical Examiner's Office of the City of New York; Dr. Henry Siegel and Dr. Irving Young, Kings County Hospital, Brooklyn; Dr. Harry Zimmerman and Dr. Harold Mamelok, Montefiore Hospital, New York; Dr. Dwight Bonham and Dr. Theodore Curphey, Mercy Hospital, Rockville Center, N. Y.; Dr. Jerome Benson, University Hospital, New York; Dr. M. Dorothea Kerr, St. Luke's Hospital, New York, and Dr. Jack Dyckman, Mount Sinai Hospital, New York.

DERMATOMYOSITIS

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DERMATOMYOSITIS is a rare disease, or syndrome, of unknown cause. The diagnosis covers a group of cases characterized by inflammation and degeneration of the skin and muscles, accompanied with severe prostration and frequently resulting in death, particularly in children and young adults. The cases so diagnosed have varied in many respects, and some writers [1] have questioned whether they form a clinical entity.

A patient recently observed at the Presbyterian Hospital, who presented most of the features included in Unverricht's original description [2] of dermatomyositis, was found at autopsy to have adenocarcinomas of the ovaries with extensive metastases. Although the coincidence of dermatomyositis and malignant disease has been reported previously, the frequency is unknown. It, therefore, seemed desirable to present a report of this case and to search the records of the Presbyterian Hospital for other similar cases. This led to a review of all cases seen at that institution over a 20-year period in an effort to throw further light on the entity.

REPORT OF A CASE

X. Y., a woman aged 46, was admitted to Presbyterian Hospital, New York, on Aug. 24, 1946. A month previously, after a week end at the seashore, erythematous blotches had appeared on the forearms and anterior portion of the neck and chest. A week later the hands were involved, and within another two days the eruption had appeared on the face in typical "butterfly" distribution. By the succeeding day, the patient had begun to feel weak and stiff all over, with soreness in the muscles, chiefly those of the thighs and shoulders. The mother and one sister had had cancer of the breast. Apart from this, the personal, family, and past history was unimportant.

Results of Physical Examination.—There were several deep red patches, with whitish centers, on the buccal mucosa. The skin of the face, neck, "V" of the chest, upper part of the back, the arms, forearms, and hands was involved in a blotchy, deep red, macular erythema. There was considerable edema about the eyes, face, and neck. The forearms felt firm and showed some scaling. No masses could be detected in the breasts or abdomen, but small axillary lymph nodes could be palpated bilaterally. Since the patient was menstruating, a vaginal examination was not performed on admission, but at a later date no abnormalities were elicited.

Pain on motion and loss of power in almost all muscle groups were prominent features. The skin and muscles were tender to touch.

From the Department of Dermatology, Columbia-Presbyterian Medical Center, New York.

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2. Unverricht, H.: Dermatomyositis acuta, Deutsche med. Wchnschr. **17**:41, 1891.

Laboratory Data.—Her blood was normal, with a noteworthy absence of leucopenia. The erythrocyte-sedimentation rate was 60 mm. per hour (Westergren). The urine showed a 1+ reaction for albumin and an occasional red blood cell. Roentgenograms of the chest, sinuses, and teeth were normal. The nonprotein nitrogen was 21 mg., serum cholesterol 312 mg., and serum protein 5.5 gm., with 4.4 gm. of albumin and 1.1 gm. of globulin per 100 cc. The cephalin-flocculation reaction was negative. Other constituents of the blood, including serum phosphatase, were normal.

In the 24-hour urine output creatine was 116 mg., and creatinine was 552 mg., giving a creatinine coefficient of 8.5 (normal, 14 to 22). This was repeatedly found.

A biopsy specimen of the muscle showed degenerative changes, with swelling and fraying of the fibers and loss of striations. Many fibers showed fragmented sarcoplasm. There was a focal infiltration of lymphocytes, and many multinucleated muscle giant cells were seen in the involved areas.

A biopsy specimen of the skin revealed an atrophic epithelium, with absence of rete pegs. Elastic fibers were scant, and there was a liquefaction degeneration, with scattered and focal collections of lymphocytes and polymorphonuclear leucocytes in the dermis. The specimens were diagnosed as completely compatible in appearance with dermatomyositis.

The electrocardiogram showed low voltage, possibly representing myocardial damage.

Course.—After a brief initial improvement, the erythema and edema of the arms increased greatly. Dyspnea and dysphagia developed; prostration was greater, and small blisters appeared on the olecranons. These disappeared gradually, and the patient's condition again improved with the administration of wheat-germ oil. However, on Sept. 23, urinary frequency and urgency developed and white blood cells were seen in the urine. These signs were interpreted as cystitis, and symptomatic treatment was given, with gradual clearing in the succeeding month. At about this time the improvement in strength and in the condition of the skin stopped, and the patient's course gradually began to go downhill. Transfusions were given without benefit. Medicaments included testosterone propionate, penicillin, and a neostigmine (prostigmin®) preparation. Streptomycin was also given without effect.

On Dec. 4 the patient suddenly displayed abdominal distention and pain in the right lower quadrant. This was treated symptomatically in the absence of any indications for surgical intervention and disappeared in a few days. The patient's general condition continued to deteriorate slowly, in spite of many medications. The erythema and the edema of the face increased, and there was some pruritus.

By March 10, 1947, portions of the erythema on the face, neck, and forearms had given way to dark reticular pigmentation, and abdominal distention became more pronounced. A week later ascites was suspected, with possible right-sided pleural effusion. On March 21, paracentesis was performed, and 4,000 cc. of clear amber fluid was withdrawn. A cell block and a pathologic analysis showed numbers (200 cells per cubic millimeter) of unclassified large basophilic cells with small granular nuclei. Culture of the fluid revealed no organisms. It was felt that polyserositis was developing on the basis of the dermatomyositic process alone, since the serum protein remained normal. The specific gravity of the fluid was 1.024. It was examined viscosimetrically (with and without hyaluronidase) and was found not to contain significant amounts of hyaluronic acid. The patient's condition continued to deteriorate, and she required further paracenteses on six occasions, the fluid being of the same character each time. New erythematous areas appeared on the upper extremities, face, and neck, and the muscle pain was so severe as to require treatment with dihydromorphinone (dilaudid®) hydrochloride.

By May 15, the patient had more or less continuous anorexia, and protein hydrolysates (amigen®) and dextrose were administered intravenously without benefit. The nonprotein nitrogen rose to 39 mg. per 100 cc., although the serum protein remained normal. Respirations ceased on June 21, 1947.

Autopsy Observations.—Bilateral ovarian adenocarcinomas, probably arising from a cystadenoma of the ovary, were present, with metastatic involvement of the peritoneal surfaces of all the abdominal viscera, the pleurae, lungs, diaphragm, and mediastinal lymph nodes. There were ascites, hydrothorax, and partial obstruction of the lower portion of the right ureter by metastatic carcinoma, with right hydronephrosis.

Severe, active dermatomyositis was present. The involved muscles showed nodular polymyositis and nodular polyneuritis.

Microscopic Examination of Skin: The epidermis of the left arm was thin, with much pigment in the basal layer. The rete pegs were flattened. No inflammation was present. Skin from the back revealed vacuolation of the epithelial cells without atrophy and without pigmentation or flat rete layer. A great deal of perivascular inflammatory reaction consisting of polymorphonuclear leucocytes was noted. The epidermis of the abdomen was thin, with increased pigment in the basal layer. The rete pegs were flattened, and there was a perivascular infiltration of lymphocytes. In skin from the thigh a ruptured vesicle (bulla?) was present. Elsewhere the intact epidermis showed hydropic degeneration, with here and there actually necrotic cells and small vesicles. In the underlying dermis were polymorphonuclear leucocytes, lymphocytes, and fibrin, with edema and dilated capillaries.

Microscopic Examination of Muscle: A specimen from the left biceps showed widespread involvement. Many muscle fibers stained lightly and had lost their cross-striations. Others, atrophic, had retracted from the sarcolemma, which was thickened. Many fibers had little or no cytoplasm, and fibrous-tissue replacement was occurring. About the blood vessels was an eosinophilic fibrinoid material. Collections of large mononuclear cells and lymphocytes could be seen between the muscle fibers. In a specimen from the pectoral region, muscle degeneration was severe, and small focal collections of lymphocytes were scattered throughout the interstitial tissue of the muscle. The rectus abdominis was less severely involved, with perineural infiltration of lymphocytes. Involvement of the muscle fibers was present in the psoas muscle. The thigh muscles (vasti) were also involved.

Comment.—The urinary frequency two months after onset of the eruption, and the autopsy observation of obstruction of the lower portion of the right ureter at the bladder wall, would seem to indicate metastatic spread at that time. Assuming that the carcinoma of the ovary was present for at least two months prior to metastasizing to the ureter, the onset of muscle pain, weakness, and rash would seem to be an interesting coincidence and suggests an interrelationship.

BRIEF REPORT OF TWO SIMILAR CASES AT PRESBYTERIAN HOSPITAL

G. B., a 53-year-old man, was admitted to the hospital on June 29, 1932. Three months previously he had had a burning, itching eruption, which began with redness around the fingernails, then spread up the arms, and gradually involved the eyelids, forehead, nose, and ears. A month after the eruption began, he noticed rather pronounced weakness first of the arms and then of the legs, together with a "thick," hoarse voice. His condition gradually worsened, and he was admitted to the Presbyterian Hospital. A series of gastrointestinal roentgenograms made at another hospital was normal.

On his admission, weakness was severe. His neck muscles were not strong enough to hold his head erect, and there was difficulty in swallowing. A dry, scaly, macular erythema was present on the arms, shoulders, and buttocks, with ill-defined margins. There was atrophy of all muscle groups. The liver extended a handbreadth below the costal margin, though the spleen could not be felt. The temperature on admission was 99 F.

Twenty-four hours after admission, the patient's temperature suddenly rose to 104 F., and he rapidly died.

Autopsy disclosed typical dermatomyositis, with pale and bloodless muscles. Microscopic observations on skin and muscle confirmed this diagnosis. There was a well-encapsulated carcinoma of the gall bladder, approximately 1.5 by 1.0 by 1.0 cm., with metastases to the abdominal lymph nodes. Suppurative appendicitis was also present.

O. O., a 55-year-old man, was admitted to the Presbyterian Hospital in May, 1945. Six weeks before admission he had gone to bed with an unusually severe infection of the upper respiratory tract and had treated himself with sulfonamides. The respiratory infection subsided, but when he tried to get up he noted great muscular weakness. This was soon accompanied with an ill-defined macular, erythematous eruption over the face, trunk, and forearms. There was stiffness of all muscle groups with great weakness, and later regurgitation of fluid through the nose occurred.

On admission, pronounced muscular weakness was present, but no appreciable muscular atrophy. There was little tenderness over the muscles and no edema. A muscle biopsy specimen was reported as disclosing dermatomyositis with typical microscopic signs. There was moderate improvement with rest in bed, and the patient was discharged home. His course in the hospital was uneventful except for drenching sweats at night.

He was readmitted in July, 1945, in considerable dyspnea. At this time a thoracentesis was done, and carcinoma cells were seen in the fluid. A roentgenogram of the chest disclosed a neoplasm of the left pleura, which was considered to be metastatic from an unknown primary site. The patient was given 1,500 r of roentgen therapy to the affected pleura but was lost to observation, and no further details are available.

CASES REPORTED IN THE LITERATURE

In the case described in detail, the coexistence of typically acute dermatomyositis and extensive metastasizing ovarian carcinoma was startling. The early writers mentioned no coincidence of dermatomyositis with malignant tumors, and Schuermann [3] noted none in the 263 cases he reviewed. However, in 1935, Bezecny [4] reported two cases of dermatomyositis, one with adenocarcinoma of the ovary, the other with a carcinoma of the breast. Other cases with coincident malignant tumors were reported by Lane [5] in 1938, Pick [6] in 1935, Gottron [7] in 1941, and McCombs [8] in 1947. Thannhauser, in discussing McCombs' case, mentioned one of his own in which there was a coincident tumor of the kidney and suggested that such association occurred more frequently than the literature indicated, and that autopsies be performed in more cases of dermatomyositis. Dostrovsky and Sagher [9] in 1946 reported on two patients, one with carcinoma of the ovary, the other with carcinoma of the breast. In the latter, changes in the skin and muscle improved after removal of the tumor and relapsed with the appearance of metastases.

In O'Leary and Waisman's series [10] of patients there was one with carcinoma of the rectum. In the 25 cases here reviewed, there were three instances of associated malignant tumors. This may be a higher rate of coincidence than would occur by chance. Becker, Kahn, and Rothman,[11] in their study of cutaneous changes associated with malignant growths, report nothing resembling dermatomyositis. Although no conclusions concerning a causal relationship can be drawn from present evidence, it should be remembered that reported autopsies in dermatomyositis are few and also that the majority of cases of dermatomyositis occur in persons below "cancer age." Additional recent reports, notably that of Quiroga,[12] described the case of a man 48 years of age who had acute dermatomyositis resulting in death, with post-mortem discovery of a pulmonary carcinoma with metastases. Sunde,[13] of

3. Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), Arch. Dermat. u. Syph. **178**:414, 1939.

4. Bezecny, R.: Dermatomyositis, Arch. Dermat. u. Syph. **171**:242 (March 16) 1935.

5. Lane, C. W.: Dermatomyositis, South. M. J. **31**:287 (March) 1938.

6. Pick, W.: Dermatomyositis, Arch. Dermat. u. Syph. **173**:302, 1935.

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9. Dostrovsky, A., and Sagher, F.: Dermatomyositis and Malignant Tumour, Brit. J. Dermat. **58**:52 (March-April) 1946.

10. O'Leary, P. A., and Waisman, M.: Dermatomyositis: Study of 40 Cases, Arch. Dermat. & Syph. **41**:1001 (June) 1940.

11. Becker, S. W.; Kahn, D., and Rothman, S.: Cutaneous Manifestation of Internal Malignant Tumors, Arch. Dermat. & Syph. **45**:1069 (June) 1942.

12. Quiroga, M. I., and Bottrich, H.: Dermatomyositis and Visceral Cancer, Prensa méd. argent. **36**:2107 (Oct.) 1949; abstracted, J. A. M. A. **142**:1028 (April 1) 1950.

13. Sunde, H.: Dermatomyositis in Children, Acta pædiat. **37**:287, 1949.

Copenhagen, described the case of an 11-year-old girl with dermatomyositis who made an apparent recovery in nine months and one year later was found to have bitemporal hemianopsia; a diagnosis of suprasellar chromophobe adenoma of the hypophysis was made, and the tumor was removed surgically. In retrospect, it was thought to have been present at the time of the dermatomyositis.

In a personal communication, Dr. A. T. Milhorat mentioned a patient of his who recovered with corticotrophin (ACTH) treatment, but relapsed and died of carcinoma of the stomach. This case was later published.[14]

Zarafonetis, Curtis, and Gulick [15] reported a case of dermatomyositis occurring in a patient who 10 months later underwent a mastectomy for carcinoma.

Certainly, cases of coincident cancer and dermatomyositis seem to be increasingly common.

ANALYSIS OF TWENTY-FIVE CASES OF DERMATOMYOSITIS SEEN AT COLUMBIA-PRESBYTERIAN MEDICAL CENTER DURING A TWENTY-YEAR PERIOD

Since 1927, the diagnosis of dermatomyositis has been made in 43 cases. In 13 of these, the diagnosis eventually was changed to that of another disease, scleroderma and disseminated lupus erythematosus for the most part. Of the remaining 30 cases, five escaped from observation and were not included in the series. This left a group of 25 cases, proved in every instance by autopsy, or biopsy, and clinical course. Of these 25 death took place in 13 after an average duration of 20 months. There were 11 autopsies, and in two cases the diagnosis was confirmed by biopsy. The 12 surviving patients were observed for an average of five years, and biopsy specimens were obtained in 10 of these.

Clinical Features.—The onset of the disease was sudden in six (24%) of these patients and gradual in 19 (76%). The presenting symptoms ranged in frequency as follows:

Tabulation Presenting Symptoms	No.	%
Swollen eyelids or rash on face	8	32
Muscular fatigue or weakness	5	20
Aching, stiff muscles	5	20
Rash on hands, then face	3	12
Sore, swollen hands	2	8
Sensitive skin	1	4
Exfoliative dermatitis	1	4

That is, the commonest presenting symptoms were dermatologic, with a rash on face or hands in 52% and other cutaneous complaints in 8%. The presenting symptoms in the remainder consisted of muscle fatigue or aching.

Muscular weakness was shown by all 25 patients, 16 complaining of pain and aching in their muscles and four complaining also of muscle tenderness. In children the weakness appeared to involve the legs first, and in adults, the neck, shoulders, and forearms more especially. Involvement of the muscles was symmetrical and bilateral. There was no spontaneous twitching. Atrophy was seen after varying

14. Oppel, T. W.; Coker, C., and Milhorat, A. T.: The Effect of ACTH on Dermatomyositis, Ann. Int. Med. **32**:318 (Feb.) 1950.

15. Zarafonetis, C. J. D.; Curtis, A. C., and Gulick, A. E.: Use of Para-Amino-Benzoic Acid in Dermatomyositis and Scleroderma: Report of 6 Cases, Arch. Int. Med. **85**:27 (Jan.) 1950.

periods in almost all cases. If the patient lived long enough, fibrosis of the muscles developed, with a tendency to contractures, although these were often overcome by good orthopedic and nursing care.

Joint stiffness and periarticular swelling occurred in seven patients, the hands, elbows, and knees being chiefly involved. Of these, three patients had actual joint changes in the hands, similar to those of rheumatoid arthritis.

Fig. 1.—Patient F. C., a 33-year-old woman. Illustration is meant to show the scaly, dry erythema of the face, with mottled pigmentation. The patient died after an illness of two and a half years with gradual onset and chronic downhill course.

Dysphagia with regurgitation of fluid through the nose, and often difficulty in coughing or talking, occurred shortly after the onset in seven patients, several of whom recovered with disappearance of this complication. In the others it was often seen as a terminal manifestation.

Serositis occurred in five patients, ascites in two (in one associated with carcinoma of the ovary), and pleural effusion in three (one of whom had carcinoma of the lung), and one patient showed generalized anasarca.

Fig. 2.—Patient F. C. Scaly, dry erythema of arm and elbow region; tenderness was a great feature, but edema was not.

Fig. 3.—Patient C. N., an 11-year-old boy (Babies Hospital); edema of the eyelids and stomatitis. The onset was acute after rubella (German measles), and recovery was complete after one year.

Eruptions of the skin of some kind occurred during the course of the disease in 24 patients, only one patient having no rash of any kind. One patient exhibited only pigmentation, which came on without noticeable erythema but with pruritus, while

another patient suffered an exfoliative dermatitis which subsided in a few months, leaving the palms and soles involved in a scaling dermatitis. The commonest type of eruption was an erythematous macular rash which was mottled or purplish, heliotrope or telangiectatic, in many cases. Table 1 shows the sites involved. Lesions on the mucous membrane of the mouth were present in four patients. There was fever of moderate degree in 14 patients. Retinal lesions occurred in one patient.

A history of exposure to sunlight was obtained from only two patients (in addition to the patient reported on in detail), both of whom exhibited bullae on exposed areas shortly after onset.

Edema was a prominent feature in 19 cases, involving the subcutaneous tissues and often coinciding with the erythematous area, but not invariably so. (See Table 2.) The edema appeared to be entirely independent of the serum protein level. Four

TABLE 1.—*Twenty-Five Cases: Distribution of Macular Erythema*

Site Involved	No. of Cases
Face	22
Eyes alone	10
Elbows and forearms	17
Hands and wrists	14
Knees	9
Legs, ankles and feet	6
Trunk	6
Neck	5
Thighs and buttocks	4

TABLE 2.—*Twenty-Five Cases: Distribution of Edema*

Site Involved	No. of Cases
Eyes	15
Face	10
Hands	8
Wrists	4
Forearms and arms	4
Knees and ankles	3

of the six cases in which edema was not a feature were later found to fit into the poikilodermatomyositis classification.

Calcifications in or under the skin appeared in four cases.

Scleroderma-like changes in the face, neck, and forearms were seen in three of our patients, and Raynaud's phenomenon was present in three others.

Laboratory Findings.—Mild anemia or none at all was the rule, with an average red-blood-cell count of 4,600,000. All patients showed a white-blood-cell count between 6,000 and 12,000, with an average of 9,300 on admission. One patient with an acute sphenoid infection later had a white-blood-cell count of 18,000, and another with peritonitis, a count of 34,000. The erythrocyte-sedimentation rate averaged 40 mm. per hour on admission but was found to be elevated in nearly every patient at some time or other during the course of the disease. Eosinophils averaged 4%, with only three patients showing counts over 10% (25, 25, and 11%). Lymphocytes ranged between 13 and 35%. Considering the normal lymphocyte range to be 20 to 40%, there was relative lymphopenia in 12 patients (that is, a count below 20%).

Albumin was present in the urine of 18 patients (the reaction was 1+ in 15 and 2+ in three) and was absent from that of the remaining seven patients. Red blood cells were observed in the urine of seven patients.

Serum calcium was normal in all patients, although it reached the upper limit of normal (11.5 mg. per 100 cc.) in those with calcifications in the skin. The serum phosphorus was determined for 11 patients and was normal. The serum proteins were normal on the whole, with two patients showing reversal of the albumin to

Fig. 4.—Patient C. N. (Babies Hospital); detail of purplish erythema over dorsa of the hands. Patient had blotchy purplish erythema of eyelids, elbows, hands, shoulders, and buttocks.

Fig. 5.—Patient C. N. (Babies Hospital); blotchy erythema over the shoulders and buttocks is well shown.

globulin ratio and the disease of both fitting into the poikilodermatomyositis classification on other grounds. Two patients showed low serum-protein levels (a total of less than 5 gm.).

The Wassermann reaction was negative in all cases.

The antistreptolysin titer was significantly raised (over 250) in three patients, each of whom was under 25 years of age and apparently recovering or with the disease in an arrested stage.

The cephalin-flocculation reaction was 2+ in two of the 10 determinations made.

Electrocardiographic examinations were performed for 17 patients, and, of these, eight showed changes suggesting myocardial damage, presumably indicating the widespread nature of the muscular involvement. Tachycardia was slightly more evident in this group than in that with normal electrocardiograms.

Microscopic Observations on Biopsy Specimens.—Skin: The observations common in these 25 cases were vacuolation of the epithelium and perivascular infiltrations

Fig. 6.—Patient M. E., an 8-year-old girl (Babies Hospital); edema of eyelids and eruption on backs of hands. Patient could ride a bicycle when last seen and seemed to be more or less recovered except for calcium deposits in the muscles, which occasionally were extruded through the skin.

of lymphocytes in the cutis. Next to these in frequency were seen atrophy of the epidermis, and, less often, flattening of the rete, and edema or fibrosis of the cutis. However, the nature of the pathologic cutaneous changes is not specific and cannot be considered diagnostic.

Muscles: The multiplicity of the muscle changes has led many investigators (e. g., Dowling [16] in England and Jager and Grossman [17] in this country) to claim that the pathologic changes are indistinguishable from those of scleroderma, thyrotoxicosis, disseminated lupus erythematosus, acute rheumatic fever, dystrophia myotonica, and other diseases. However this may be, in the present cases the common observations were (1) increase in muscle nuclei (i. e., in muscle cells beneath the sarcolemmic membrane, which may not be actually increased, perhaps, but represent rather an accumulation of nuclei in a fiber from which protoplasm has largely disappeared); (2) a perivascular infiltrate consisting mostly of lymphocytes, with monocytes, polymorphonuclear leucocytes, plasma cells, and occasionally histiocytes also being found; (3) a perivascular increase in interstitial tissue; (4) degenerative changes in the muscle fibers, such as loss of striation, vacuolation, fragmentation and atrophy, homogenization, and even fibrosis. The inflammatory features seemed somewhat secondary to the degenerative features in these 25 cases. As a rule, the paucity of vascular changes, especially in the interseptal blood vessels, served to distinguish the disease from scleroderma, although on occasion this may be a difficult or an impossible distinction.

Creatinuria.—Steinitz and Steinfeld [18] recorded creatinuria in a case of dermatomyositis in 1931, and, on the evidence of many subsequent observers, it is a practically constant finding in this disease. Jager and Grossman [17] reported a diminished creatine content in the involved muscles. Creatinuria occurs also in other myopathies, in starvation, in such diverse conditions as thyrotoxicosis and Addison's disease, and in trichinosis. It is evidence of muscle degeneration but points to no specific cause.[19] It may, however, be useful in differentiating dermatomyositis from lupus erythematosus or scleroderma, though it does occur frequently in the two latter diseases.[20] The normal adult human being has approximately 450 mg. of creatine per 100 gm. of muscle tissue. In all patients of the present series in whom muscle creatine was studied, it was found to be well below this point (about 200 mg. per 100 gm.). Normally in the male creatine is not excreted in the urine, though there may occur daily creatinine (anhydride of creatine) excretion of 1 to 2 gm. in the 24-hour specimen. If one disregards creatine occurring in the urine in women, as it often normally does, and in children, as it always does, creatinuria per se can be regarded as of significance only in adult males, in whom it signifies increased endogenous protein catobolism, i. e., muscle destruction.[19] If creatinuria occurs, it does so at the expense of the 24-hour excretion of creatinine, which is thereby lessened. Hence, the creatinine coefficient, the milligrams of creatinine per kilogram

16. (*a*) Dowling, G. B., and Griffiths, W. J.: Dermatomyositis and Progressive Scleroderma, Lancet **1**:1424 (June 24) 1939. (*b*) Dowling, G. B.: Generalized Scleroderma, Brit. J. Dermat. **52**:242 (Aug.-Sept.) 1940.

17. Jager, B. V., and Grossman, L. A.: Dermatomyositis, Arch. Int. Med. **73**:271 (April) 1944.

18. Steinitz, H., and Steinfeld, F.: Untersuchungen zur Kreatinstoffwechsel bei Dermatomyositis, Ztschr. ges. exper. Med. **79**:319, 1931.

19. Bodansky, M.: Introduction to Physiological Chemistry, ed. 3, New York, John Wiley & Sons, Inc., 1934.

20. Lamb, J. H.; Lane, E. S.; Keaty, C., and Hellbaum, A.: Steroid Hormones: Studies in Dermatomyositis, Lupus Erythematosus and Some Light Sensitive Dermatoses, Arch. Dermat. & Syph. **57**:785 (May) 1948.

of body weight excreted in the 24-hour output of urine, is lowered in myopathies. If the normal coefficient is considered to be 18 to 32 mg. in an adult male, the coefficient should be under 18 mg. in the presence of dermatomyositis.

It is worth mentioning that creatinuria is normally found in eunuchs and can be easily induced in aged men or others with absent testicular function.

Lamb and his co-workers showed the beneficial effect of testosterone therapy on the clinical course of dermatomyositis and also demonstrated its effect in decreasing creatinuria in four patients.[20] This result was probably due to the nitrogen-retaining power of testosterone. As creatine metabolism is still not clearly understood, the role of creatine in dermatomyositis is obscure.

Mortality.—Of this group of 25 patients, 13 died, a figure which bears out the often-reported 50% mortality. From this breakdown, it appears that the majority of the patients who live past the first year ultimately survive. Also, those who run an acute, fulminating course have a poorer prognosis. O'Leary and Waisman[10] found that the tempo of onset predicted the course fairly well. In this series the suddenness of onset did not seem closely related to the prognosis. Sudden onset occurred in six cases with only one death, and gradual onset, in 19 cases with 12

TABLE 3.—*Relation of Mortality to Duration*

Duration	6 Mo.	7-12 Mo.	1-2 Yr.	2 Yr. +
Died	5	5	0	3
Disease arrested	2	3	5	2

TABLE 4.—*Relation of Mortality to Age*

Age, Yr.	Under 10		11-20		21-30		31-40		41-50		51 +	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Died	3	75	2	66	2	40	1	20	1	25	2	50
Total	4		3		5		5		4		4	

deaths. From this table it can be seen that in the lower age groups the mortality is high, decreasing until the sixth decade, when it rises again. The percentages are only approximations, since the group is so small.

COMMENT

A. *Acute Dermatomyositis.*—The concept of dermatomyositis as a disease entity dates perhaps from a case of acute degenerative disease of the muscles, which apparently belongs to this group, reported by Wagner in 1863.[21] A more circumstantial description was given by Wagner in 1887, that of a 24-year-old man who died in six weeks of an acute progressive polymyositis accompanied with slight swelling of the face and extremities.[22] Unverricht differentiated the disease in his case from poliomyelitis, trichinosis, periarteritis nodosa, peripheral neuritis, and Zenker's post-typhoid degeneration of muscle. In 1891 [2] he reported a second case with recovery and gave the name dermatomyositis to the disease. Hepp [23] described a similarly fatal case in the year that Unverricht described his first case, 1887.

21. Wagner, E.: Fall einer seltenen Muskelkrankheit, Arch. Heilk. **4**:282, 1863.
22. Wagner, E.: Ein Fall von acuter Polymyositis, Deutsches Arch. klin. med. **40**:241, 1886.
23. Hepp, P.: Pseudotrichinosis, Klin. Wchnschr. **24**:297, 1887.

In 1901 Steiner [24] reported a case and collected from the literature 27 others which he regarded as typical. Many acute cases appear in more recent reports.[25] A case described by Leys [26] had several features rather similar to those seen in dermatomyositis, as did Williams' [27] five cases of "epidemic myositis," which he referred to as dermatoneuromyositis. Both these reports concern an acute illness with quick recovery.

B. *Chronic Dermatomyositis or Poikilodermatomyositis.*—Steiner regarded the subacute or chronic examples which he included in his series as of the same disease as the acute and fatal cases. In the subacute cases, the early dermatitis was replaced by pigmentation and the muscles showed fibrosis.

Petges and Clejat [28] in 1906 reported a case of this type as "atrophic sclerosis of the skin with generalized myositis." In 1929 Petges and Petges [29] applied the name poikilodermatomyositis to the group of chronic cases with insidious onset because of similarities to Jacobi's case,[30] about which more will be mentioned later.

C. *Poikiloderma Atrophicans Vasculare.*—Under this diagnosis, Jacobi in 1908 [30] reported the case of a 30-year-old man with joint pains, progressive weakness and wasting of the muscles, loss of subcutaneous fat, and extensive atrophy of the skin with mottled pigmentation, depigmentation, telangiectasis, capillary hemorrhages, some desquamation, and partial alopecia. The cutaneous picture resembled that of atrophy following roentgen irradiation. Jacobi differentiated his case from that of Petges and Clejat [28] because, in spite of the weakness, he could find no myositis. Lane [30a] revived interest in this syndrome by a detailed description of a similar case. Gougerot and Eliascheff in 1929 [31] attempted to define the disease more exactly by emphasizing the miliary lichenoid papules, the desquamation, telangiectasis, petechial hemorrhages, pigmented macules, atrophy, and absence of sclerosis. Since then a number of cases has been reported under this ill-defined diagnosis. More recently a case [31a] has been described fulfilling all the criteria of Jacobi, in which later full-blown

24. Steiner, W. R.: Dermatomyositis: Case Report and Review of the Literature, J. Exper. Med. p. 407, 1901-1905.

25. Steiner, W. R.: Report of 2 Cases of Dermatomyositis, J. A. M. A. **78**:271 (Jan. 28) 1922.

26. Leys, D.: Acute Benign Dermatomyositis, Brit. M. J. **2**:636 (Nov. 28) 1942.

27. Williams, D.: Epidemic Myositis, with Neuritis, Erythema, and Meningeal Symptoms, Quart. J. Med. **10**:283, 1941.

28. Petges, G., and Clejat, C.: Sclérose atrophique de la peau et myosite généralisée, Ann. dermat. et syph. **7**:550, 1906.

29. Petges; Nougneau; Lecoulant, and Delas: Poïkilodermie et polymyosite (poikilodermatomyosite), Bull. Soc. franç. dermat. et syph. **36**:817, 1929. Petges, G., and Petges, A.: Poïkilodermatomyosite, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, Vol. 6, p. 153.

30. Jacobi, E., and Freiburg: Poikiloderma atrophicans vascularis, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1908, Vol. 3, pp. 95-100.

30a. Lane, C. G., in discussion on Guy, W. H.; Grauer, R. C., and Jacob, F. M.: Poikilodermatomyositis, Arch. Dermat. & Syph. **40**:867 (Dec.) 1939.

31. Gougerot, H., and Eliascheff, O.: Premier cas français de myxoedema tuberosum de Jadassohn-Doesseker, Bull. Soc. franç. dermat. et syph. **36**:148 (March) 1929.

31a. Bloom, D.: Poikiloderma Vasculare Atrophicans with the Histologic Picture of Mycosis Fungoides, read before the Atlantic Dermatological Conference, March 8, 1947. There were at least 15 other case presentations in the three or four years before this.

mycosis fungoides developed. The existence of such an entity as poikiloderma atrophicans vasculare seems open to question.

In 1902 Thayer [32] described a case, differing somewhat from those of Unverricht and Hepp, as an instance of polymyositis hemorrhagica, and Bodansky [33] reported a case of myositis fibrosa.

The relationship of these three groups of cases is not clear. Petges and Petges in 1929 believed that "acute polymyositis of Unverricht, Wagner, and Potain" must be differentiated sharply from the chronic disease, which they considered a myosclerosis. They divided the latter into three groups: (1) poikiloderma without muscle involvement, (2) poikilodermatomyositis, and (3) poikilodermatomyositis with calcification. Dowling and Freudenthal in 1938,[34] on the basis of clinical and histologic evidence, concluded that dermatomyositis and poikiloderma were distinct and unrelated conditions which might occur together. They considered that the types of the former, described by Unverricht and by Petges, comprised a clinical entity. This point of view has been followed by most subsequent observers. At first sight, there seems little similarity between the cases beginning with sudden erythema of the face and extremities, edema (especially of the eyelids), rapid degeneration and infiltration of the muscles, immediate prostration, and death within three to 12 months (the Unverricht type), and others with insidious onset, gradually increasing atrophy, pigmentary changes of the skin of the arms and upper part of the thorax, and fibrosis and atrophy of the muscles. There are, however, cases which begin with acute, edematous, and infiltrated lesions and pass to a chronic stage with atrophy and fibrosis.

In this series of 25 cases six could be said to be of gradual onset and of chronic character, accompanied with pigmentation and atrophy of the skin. There were subcutaneous calcifications in four cases, reversal of the albumin to globulin ratio in two, and a distinctive type of dermatitis, resembling x-ray dermatitis or dermatitis medicamentosa due to gold, in two instances. One patient gave a history of pigmentation coming on after pruritus, which has been said to be characteristic of poikilodermatomyositis. There was no history of edema in three of the cases. While all these points have been mentioned as serving to place such cases in the poikilodermatomyositis classification or subgroup, similar cutaneous lesions are seen in all cases of dermatomyositis of long standing, especially arrested cases, in which there is almost always pigmentation, and occasionally atrophy indistinguishable from that described by Petges and Petges. Those patients whose dermatomyositis became arrested and who survived often had a chronic, smouldering course. Among the 12 surviving patients, the course covered an average of three years and sometimes reached five, the average period of observation being five years.

Efforts to find other distinguishing features which would serve to characterize a group as distinctly poikilodermatomyositis were futile. In the six cases mentioned the patients' ages ranged from 21 to 59 years, the average being 37. The mortality rate was 50%, and the duration of activity of the disease averaged five years. The

32. Thayer, W. S.: Notes on a Case of Acute Hemorrhagic Poliomyelitis, Boston M. & S. J. **147**:1, 1902.

33. Bodansky, M.; Schwab, E. H., and Brindley, P.: Myositis Fibrosa, J. Biol. Chem. **85**:307 (Dec.) 1929.

34. Dowling, G. B., and Freudenthal, N.: Dermatomyositis and Poikiloderma, Brit. J. Dermat. **50**:519 (Oct.) 1938.

cutaneous changes were not vastly different. I gained the impression that those cases referred to as poikilodermatomyositis are, for the most part, cases of dermatomyositis of gradual onset and chronic course.

ETIOLOGIC CONSIDERATIONS

A. *Infection.*—Dermatomyositis is a nonpurulent polymyositis with inflammation in the skin and degeneration of muscle. O'Leary and Waisman [10] took muscle cultures in 17 instances and in five grew a Streptococcus which, when inoculated into animals, produced hemorrhagic lesions of the skin and muscle in three cases. They also cultured a Streptococcus from the nasopharyngeal secretions in six cases which caused hemorrhagic lesions in the muscles of rabbits. This work suggests an infectious cause, which Stuckey [35] feels is also borne out by the following features: onset often after a febrile illness; the occurrences in some cases of fever, albuminuria, or splenomegaly, and the relapsing nature of the disease. Greenaway and Lambie [36] carried out extensive virus studies with negative results. They concluded that the disease is not infectious. Madden [37] presented a case of dermatomyositis in a 13-year-old schoolboy in whom the disease remained quiescent while penicillin was being administered but relapsed as soon as use of the drug was discontinued. Other authors (e. g., Cornbleet [38]) have had occasional success with penicillin therapy. Clark [39] describes a case in which recovery was possibly attributable to sulfadiazine treatment.

Most theories of the cause have involved infection, although pathologists have differed as to whether the early lesions were inflammatory or purely degenerative. Weber [40] interpreted the lesions as "toxic effects of an infection" which were followed by degenerative changes. In O'Leary and Waisman's series,[10] 11 cases followed an acute infection.

Of Jager and Grossman's cases,[17] two followed tooth extraction and two a febrile illness. In one of Wolf and Wilens' [41] cases, a pericecal abscess was observed at autopsy, along with an early carcinoma of the gallbladder, without metastases, and in another case there was a peritonsillar abscess. In 1934 McGarrahan [42] described cutaneous reactions indicating hypersensitivity to Staphylococcus in his case. There was a coincidental eosinophilia of about 20% which dropped to 5% after treatment with autogenous vaccine (from nose).

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35. Stuckey, E. S.: Dermatomyositis: Summary of Literature and Case Report, Brit. J. Dermat. **47**:85 (March) 1935.

36. Greenaway, T. M., and Lambie, C. G.: Dermatomyositis, Brit. J. Dermat. **49**:209 (May) 1937.

37. Madden, J.: Dermatomyositis: Case Presentation, Arch. Dermat. & Syph. **53**:519 (May) 1946.

38. Cornbleet, T.: A Case for Diagnosis, Arch. Dermat. & Syph. **55**:570 (April) 1947.

39. Clark, N. S.: Dermatomyositis in Childhood (4 Cases), Arch. Dis. Childhood **21**:160 (Sept.) 1946.

40. Weber, F. P., and Gray, A. M. H.: Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), Brit. J. Dermat. **36**:544 (Dec.) 1924.

41. Wolf, A., and Wilens, S. L.: Two Cases of Dermatomyositis with Post-Mortem, Am. J. Path. **12**:239 (March) 1936.

42. McGarrahan, J. C.: A Case of Dermatomyositis Following Influenza, J. A. M. A. **102**:680 (March 3) 1934.

In the present series of 25 cases, five occurred during or after an infection (measles, one; abortion, one; urethritis, one; acute sphenoid sinusitis, one, and chronic purulent ethmoiditis, one). Two additional patients showed evidence of pulmonary tuberculosis.

B. *Light Sensitivity.*—Banks [43] drew attention to the relationship between exposure to sunlight and the onset of the disease, as did Turner.[44]

C. *Allergy.*—Three of our patients gave evidence of an allergic background: One had a history of gonorrheal arthritis and diarrhea from milk; in one, the onset followed injections for hay fever, and one had an exacerbation of her dermatomyositis every time she ate grapefruit. This was repeatedly demonstrated, improbable as it seems. The allergic factor has not been emphasized by most writers on this disease.

D. *Vitamin Factors.*—The work of Milhorat and associates [45] on the effect of wheat germ on creatinuria in cases of dermatomyositis and progressive muscular dystrophy is possibly significant. Wolbach's [46] work on ascorbic acid and its effect on the ground substance is also of probable importance. Silverman and Powell,[47] as well as Jager and Grossman,[17] have drawn attention to vascular changes occurring in the disease, as has Turner.[44]

Goettsch and Pappenheimer [48] found that they could produce degeneration in the voluntary muscles, except for the heart and diaphragm, of the guinea pig and rabbit, but not of the rat. They used a diet adequate in everything but vitamin E. When these changes became evident, they could not be reversed on addition of vitamin E to the diet. Milhorat believes that such changes are due not to a straight defect, but rather to a metabolic upset. He suggests that the tissues have a deficiency of pigmentation in vitamin-E deficiency and in dermatomyositis. There seem to be definite cyclic changes in vitamin-E metabolism in the human being.[49]

E. *Endocrine Considerations.*—Petges and Petges emphasized endocrine factors. Dowling [16] believed the eye-muscle lesions of dermatomyositis and scleroderma were similar to those seen in thyrotoxicosis, but little clinical evidence of thyroid disease has been found in dermatomyositis. The absence of thyroid disease is perhaps an argument against a gonadal cause, as had been suspected in lupus erythematosus, though Griffiths [50] concluded that the metabolic changes in dermatomyositis were strikingly similar to those seen in endocrine diseases, such as acromegaly and pituitary basophilism.

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43. Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, Libman-Sachs Syndrome and Periarteritis Nodosa? New England J. Med. **225**:433 (Sept. 18) 1941.

44. Turner, J. C.: Dermatomyositis: Study of 3 Cases, New England J. Med. **216**:158 (Jan. 28) 1937.

45. Milhorat, A. T.; Toscani, V., and Bartels, W. E.: Dermatomyositis, and the Effect of Wheat Germ on Creatinuria, Proc. Soc. Exper. Biol. & Med. **58**:40 (Jan.) 1945.

46. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. & Lab. Med. **1**:1(Jan.) 1926; Controlled Formation of Collagen and Reticulum, Am. J. Path. (supp.) **9**:689, 1933.

47. Silverman, J. J., and Powell, V. E.: Dermatomyositis, Peripheral Vascular Changes, Am. Heart J. **30**:441 (Nov.) 1945.

48. Goettsch, M., and Pappenheimer, A. M.: Nutritional Muscular Dystrophy in Guinea Pig and Rabbit, J. Exper. Med. **54**:145 (Aug.) 1931.

49. Milhorat, A. T.: Personal communication to the author.

50. Griffiths, W. J.: Biochemical Aspects of Dermatomyositis, Brit. J. Dermat. **52**:295 (Oct.) 1940.

Among the cases here reviewed, in three possible endocrine disturbance was seen. In one an 8-year-old girl had pubic hair and enlarged breasts and a family history of precocious sexual development. One patient had a large ovarian cyst, and in one amenorrhea developed after a motor-car accident preceding the onset of her dermatomyositis. Lamb [20] has drawn attention to the correlation between time of onset of many skin diseases and an epoch of life in which hormonal balances are undergoing change. In two of the four patients with dermatomyositis (one male and three female) who were helped by testosterone injections and high-protein and vitamin intake, there had been menstrual flooding a few months before onset. It seems impossible to avoid the suspicion of some sort of endocrine connection, especially of a gonadal nature, though as yet the connection is far from clear.

F. *Hyaluronic Acid.*—Meyer [51] has recently stated that hyaluronic acid and chondroitin sulfate must be regarded as essential components of the interfibrillar ground substance (cement substance) of striated muscle, fascia, tendons, and skin. Robb-Smith [52] studied the effect of hyaluronidase on guinea-pig muscle and showed that the collagen was not affected, though the reticulin membranes became separated from the muscle fibers. Klemperer [53] has drawn attention to the homogeneous ground substance and its importance in this group of diseases (lupus erythematosus, scleroderma, dermatomyositis, etc.). He mentioned that Selye has provoked mucinous edema of the skin in hairless mice by repeated applications of estradiol and cited Leo Loeb as producing hyaline changes in the stroma of various organs by the repeated injections of estrogen.

It is probable that the ground substance is composed of a variety of mucoproteins the colloidal state of which is affected in one direction by enzymes, such as hyaluronidase, the estrogens appearing to have an opposite influence.[54]

RELATIONSHIP TO OTHER COLLAGEN DISEASES

Keil's[55] description of the dermatomyositis facies as being "swollen eyelids with heliotrope cheeks" seems apt. In differential diagnosis lupus erythematosus is one of the principal diseases to be excluded. However, this disease does not affect the eyelids in the early stages. Dermatomyositis also may commence with erythema across the cheeks in "butterfly" distribution, but this is usually more inflammatory than in lupus erythematosus, and, while it may be telangiectatic, the eruption does not show the adherent scales of the latter. Scaling may occur in dermatomyositis, but it is faint and often evanescent, leaving pinhead to lentil-sized areas of atrophy. The erythema often gives way to a reticulated pigmentation of the eyelids, earrims, and nape of the neck especially, and sometimes also over the small joints of the hand.

51. Meyer, K.: Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335 (July) 1947.

52. Robb-Smith, A. H. T.: Tissue Changes Induced by Cl. Welchii Type A Filtrates, Lancet **2**:362 (Sept. 22) 1945.

53. Klemperer, P.: Pathogenesis of Lupus Erythematosus and Allied Conditions, Ann. Int. Med. **28**:1 (Jan.) 1948.

54. Sprunt, D. H.; McDearman, S., and Raper, J.: Studies on Relationship of Sex Hormones to Infection: Effect of Estrogenic and Gonadotropic Hormones on Vaccinia and the Spreading Factor, J. Exper. Med. **67**:159 (Jan.) 1938. Sprunt, D. H., and McDearman, S.: Hyaluronidase, Endocrinology **27**:893 (Dec.) 1940.

55. Keil, H.: Manifestations in Skin and Mucus Membrane in Dermatomyositis, with Reference to the Differential Diagnosis from Lupus Erythematosus, Ann. Int. Med. **16**:828 (May) 1942.

Petges has drawn attention to the mask-like rigidity of the face, which suggests scleroderma. Often the cheeks are brown and squamous, and the skin is thick and stretched. Variegated patches with brownish macules, uneffaced by pressure, may be found on the neck, chest, and forearm. The epidermis is often harsh and scaly, particularly on the extensor aspects of the limbs. Occasionally there is a cyanotic erythema of the finger tips, resembling that seen in lupus erythematosus. On the face there may be scales and white shiny spots, mingled with pigmentation and erythema.

Dowling and Freudenthal [34] felt that after the edematous phase there was a uniform progression of cutaneous changes from face to neck, from neck to thorax, to shoulders, arms, and backs of the hands. This was seen in only one of the present patients. Several patients, however, showed as prodromes the patchy, evanescent erythemas of the trunk which Dowling has also mentioned.

The acute cases of dermatomyositis (Unverricht type) show many similarities to disseminated lupus erythematosus, such as erythema of the cheeks, telangiectatic lesions of the phalanges, vague arthralgias, prostration with irregular or absent fever, and occasional onset after exposure to the sun. Histologically, the early cutaneous lesions are often indistinguishable. On the other hand, the presence of myositis, the almost constant presence of edema of the eyelids, the early involvement of the hands, neck, and thorax, the absent leucopenia, the lack of sex preponderance, and, most important, the relatively low mortality (50%) seem significant differences. Recent evidence that lupus erythematosus responds dramatically to cortisone or corticotrophin (ACTH) treatment, whereas dermatomyositis is less regularly influenced, indicates an important difference in their pathogenesis.

On the other hand, Weber and Gray [40] described as "chronic relapsing polydermatomyositis with predominant involvement of the subcutaneous fat" the first recorded case of this syndrome, now generally considered a separate entity and known as chronic nonsuppurative panniculitis of Weber and Christian. Dowling in 1940,[16b] emphasizing the sclerotic changes in chronic cases and the occasional report of Raynaud's phenomenon as an initial symptom, concluded that dermatomyositis and scleroderma are one disease. Banks in 1941 [42] went farther and stated that disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, and scleroderma were distinct syndromes, and that patients frequently present features of two or more of them. He concluded that all represented widespread vascular involvement, differing in the extent of the pathologic change, the size of the vessels involved, and the organs chiefly affected. Since his paper appeared, the use of the term "collagen disease" to include all these syndromes has become increasingly popular.

Such a generalization certainly simplifies the problem of diagnosis but does not help in the problem of prognosis or in the guiding of treatment. It may well hinder the recognition of an etiologic factor which may be present in one group but not in others, if in reality they are distinct diseases.

Although no striking conclusions emerge from the factors associated with the onset of dermatomyositis, there exists the likelihood that a common process is active in all cases. This is a disease of unknown cause, characterized chiefly by morphologic changes of skin and muscle with no highly distinctive characteristics. A definite conclusion concerning the relationship seems impossible. However, is it conceivable that carcinoma and an acute sphenoid infection can produce a similar disease pic-

ture? Perhaps, if the sphenoid infection is due to a hyaluronidase-producing Streptococcus and the tumor produces beta glucuronidase in sufficient quantity, there is some understandable connection. Such speculation is intriguing, if inconclusive.[56]

TREATMENT

To say that treatment has been relatively ineffective to date is certainly an understatement. A ray of hope emerges with the reports of corticotrophin therapy in children,[57] with or without subsequent testosterone therapy. Certainly if treatment is begun early in the inflammatory period, and no underlying hidden malignant tumor is present,[14] there is possibly better than a 50% chance of arresting the disease. Treatment over a long period is necessary and maintenance dosage desirable in all cases, especially in those of adults.[58] The reports of success with large doses of *p*-aminobenzoic acid are encouraging.[15]

SUMMARY

Dermatomyositis is a disease affecting the skin and muscle, usually with a gradual onset. It tends to run a short course with high mortality in children and young adults and a longer course with eventual recovery in older adults.

An analysis of the symptoms and findings in 25 cases of dermatomyositis, with a more complete report of one case, is given. Many factors felt to exert an influence on the disease are discussed.

A search for malignant tumors, focal infection, and endocrine disturbances should be made in every case of dermatomyositis.

Prof. J. Gardner Hopkins and Miss Janet Newkirk, of the Department of Dermatology, Columbia University College of Physicians and Surgeons, assisted in the preparation of this paper. The cases were drawn from the Presbyterian Hospital, Babies Hospital, Neurological Institute, and Harkness Pavilion of the Columbia-Presbyterian Medical Center. The work took place by permission of the late Prof. A. Benson Cannon, Chief of Dermatology.

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56. Fishman, W. H.: Beta-Glucuronidase Activity in Tumor Tissue, Science **106**:66 (July 18) 1947. Kasden, S. C.; Fishman, W. H., and Hamburger, F.: Beta-Glucuronidase Studies, J. A. M. A. **144**:892 (Nov. 11) 1950. Brock, W. G.: Dermatomyositis, Proc. Staff Meet., Mayo Clin. **9**:147 (March 7) 1934.

57. Thorn, G. W., and others: Clinical Uses of ACTH and Cortisone, New England J. Med. **242**:783 (May 18); 824 (May 25); 865 (June 1); 829 (May 25) 1950.

58. Ragan, C.: Effect of ACTH on Dermatomyositis, in Proceedings of First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 423. Elkinton, J. R., and others: Effects of ACTH Therapy, J. A. M. A. **141**:1273 (Dec. 31) 1949. Elkinton, J. R., and others: Effects of ACTH with Collagen and Allied Diseases, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 429.

STRUMA LYMPHOMATOSA (HASHIMOTO'S STRUMA)

Review of Fifty-One Cases with a Discussion of the Endocrinologic Aspects

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SINCE the original description of struma lymphomatosa by Hashimoto in 1912, much confusion has arisen in the literature concerning the diagnosis, pathology, and therapy of this clinicopathologic entity. The present study is a review of 51 cases of struma lymphomatosa seen at the Massachusetts General Hospital. Since the literature is lacking in reports of some of the newer laboratory methods of studying thyroid function in struma lymphomatosa, it is one of the purposes of this paper to describe such observations. Serum protein-bound-iodine determinations, radioactive-iodine (I^{131}) tracer studies, and radioautographs were obtained on several of the patients in the present series. These help to throw additional light on a number of current problems.

The etiological basis of struma lymphomatosa is unknown. Various theories have been advanced to explain the picture of this entity. These hypotheses will be mentioned later in the section under Comment.

METHODS AND CLASSIFICATION OF MATERIAL

There are many excellent reviews concerning the controversy regarding the unitarian concept of Riedel's struma (chronic thyroiditis) and Hashimoto's struma.[1] The weight of recent opinion favors the idea that these are separate entities. We are in accord with this view. Hence, cases of Riedel's struma have been omitted from this series. In addition, we have regarded struma lymphomatosa and lymphadenoid goiter as minor variations of the same pathologic picture.

PATHOLOGIC ASPECTS

Between the years 1930 and 1949, the pathologic diagnosis of chronic thyroiditis was made 140 times at the Massachusetts General Hospital. This number included 63 cases of Hashimoto's struma, 61 cases of so-called nonspecific chronic thyroiditis,

From the Thyroid Clinic and Pathology Department, Massachusetts General Hospital.

1. (*a*) Vaux, D. M.: Lymphadenoid Goiter: Study of 38 Cases, J. Path. & Bact. **46**:441-445 (May) 1938. (*b*) Lee, C. M., Jr., and McGrath, E. J.: Struma Lymphomatosa (Hashimoto), Surgery **2**:238-246 (Aug.) 1937. (*c*) Womack, N. A.: Thyroiditis, ibid. **16**:770-782 (Nov.) 1944. (*d*) McClintock, J. C., and Wright, A. W.: Riedel's Struma and Struma Lymphomatosa (Hashimoto), Ann. Surg. **106**:11-32 (July) 1937. (*e*) Rabson, S. M., and Arata, J. E.: Hashimoto's and Riedel's Struma and Lymphadenoid Goiter, Am. J. Clin. Path. **19**:750-764 (Aug.) 1949.

and 16 cases of Riedel's struma. A review of both clinical and pathologic data on all the patients in the group with Hashimoto's struma was made. In addition, the microscopic sections from those cases listed as nonspecific chronic thyroiditis and those of Riedel's struma were restudied. This reanalysis, utilizing uniform criteria, resulted in confirmation of the diagnosis of Hashimoto's struma in a total of 51 cases during the 20-yr. period. A total of 3,676 thyroid operations of all kinds was performed in this time, and the 51 instances of operation for struma lymphomatosa constitute 1.4% of all thyroidectomies. The incidence of struma lymphomatosa, as published by various authors, is usually given as about 1% but varies from 0.3 to 1.27%.[2]

The 51 cases were arbitrarily divided into two groups, as follows:

Group I: Cases which were typical in all respects of the generally accepted concepts of the clinical picture and the gross and microscopic pathologic observations. This group contained 44 cases.

Group II: Cases which had some atypical feature or features in either the clinical or the pathologic picture and thus might conceivably be rejected as equivocal cases by some investigators. This group contained seven cases.

Cases with clinical evidence of thyrotoxicosis and those in which the changes were confined to a single large nodule (adenoma) were omitted. Included in Group II, however, were cases in which the disease was marked on one side of the thyroid gland only but in which the surgeon also noted abnormality of the opposite side, yet only unilateral subtotal thyroidectomy was performed.

Grossly, the thyroid of struma lymphomatosa presents a uniform enlargement which is most characteristically bilateral. The surface is encapsulated, smoothly lobulated, and paler than normal, varying from tan-red to yellowish-pink (Fig. 1). The gland's consistency is uniformly firm, often being described as "rubbery" in the pathologist's description. In 37 subtotal thyroidectomies in this series, the weights of 32 glands were recorded, with an over-all average of 66.8 gm. The largest specimen weighed 225 gm. The average weight of the normal thyroid in women of the fifth decade is about 20 gm., according to Parmley and Hellwig.[3] On cross section, the thyroid of typical Hashimoto's struma shows a homogeneous appearance, with glistening yellowish-pink to tan tissue, separated into lobulations by fibrous septa. The fresh tissue often bears a striking similarity to the translucent-like surface of a hyperplastic lymph node. Normal colloid-containing thyroid parenchyma is not grossly recognized in most cases. Occasional adenomas or discrete nodules are encountered but, in the words of Graham,[4] appear as "an

2. (*a*) McSwain, B., and Moore, S. W.: Struma Lymphomatosa (Hashimoto's Disease), Surg., Gynec. & Obst. **76**:562-569 (May) 1943. (*b*) Patterson, H., and Starkey, G.: Clinical Aspects of Chronic Thyroiditis, Tr. Am. S. A. **66**:437-450, 1948; Ann. Surg. **128**:756-769 (Oct.) 1948. (*c*) Joll, C. A.: Pathology, Diagnosis and Treatment of Hashimoto's Disease (Struma Lymphomatosa), Brit. J. Surg. **27**:351-389 (Oct.) 1939. (*d*) Marshall, S. F.; Meissner, W. A., and Smith, D. C.: Chronic Thyroiditis, New England J. Med. **238**:758-766 (May 27) 1948.

3. Parmley, C. C., and Hellwig, C. A.: Lymphadenoid Goiter: Differentiation from Chronic Thyroiditis, Arch. Surg. **53**:190-198 (Aug.) 1946.

4. Graham, A.: Struma Lymphomatosa (Hashimoto), Tr. Am. A. Study Goiter, 1940, pp. 222-251.

inconspicuous part of the disease." Noteworthy is the absence of adherent fragments of perithyroid muscle and fascial structures to the thyroid capsule.

The microscopic picture of Hashimoto's struma is reasonably distinctive, but the individual histologic features are not specific for this entity. Because of this lack of specificity, there has naturally arisen confusion concerning the criteria used to distinguish such cases from other pathologic thyroid states which share, in some degree, similar pathologic features. In brief, cases were considered as possibly being examples of struma lymphomatosa on histologic grounds only when the microscopic picture revealed the following signs: a diffuse dissemination of lymphoid tissue, with lymphoid follicle formation; extensive areas of parenchymal degeneration; an absence of large areas of scarring or actively sclerosing fibrosis, and an absence of any nonlymphoid cellular infiltrate (such as polymorphonuclear leucocytes, plasma cells, or giant cells), which might be indicative of some form of

Fig. 1 (Case 15).—Surgical specimen of Hashimoto's struma, weight 225 gm. Note the prominence of the lobulations, the diffuseness of the enlargement, and the pale surface.

unknown inflammatory response. The cases which did not fulfil these general criteria, recognized by the majority of other observers,[5] were immediately discarded from consideration as possible examples of Hashimoto's struma. Those cases which met these general histologic requirements to a minor extent, so as to place them in a questionable light, were included in the noncommittal category of chronic thyroiditis, nonspecific type. A few cases were encountered in review of the instances of Hashimoto's struma which might not meet rigid requirements of some students of this disease, but which in our opinion could not be satisfactorily classified otherwise. These cases have been alluded to above and appear under the heading "Group II: Hashimoto's struma."

The most outstanding microscopic feature in struma lymphomatosa is the lymphoid tissue, which is distributed quite diffusely throughout the thyroid gland. This lymphoid infiltration often varies in intensity from one area to another in

5. Joll.[9c] Graham.[4]

the same gland, ranging from dense aggregates of lymphocytes with germinal-center formation to light sprinklings of lymphocytes within the interfollicular spaces of the remaining parenchyma. Regardless of other microscopic features or clinical factors in favor of the diagnosis of struma lymphomatosa, no case was included in the series which did not exhibit an impressive degree of lymphoid infiltration with actual follicle formation.

Associated with the lymphoid changes are extensive evidences of parenchymal degeneration. The most outstanding of these alterations are small follicles largely devoid of colloid, swollen thyroid cells exhibiting the cytoplasmic oxyphilia and nuclear pleomorphism of atrophy, actual loss of follicle arrangement of disintegrating cells, and zones of almost obliterated thyroid tissue recognizable only by faint cellular and acinar outlines in a sea of lymphocytes. The paucity of significant zones of healthy parenchyma is a constant observation, but when such zones are present, they often reveal hyperplastic changes of the thyroid follicles. These hyperplastic foci seem best explained on the basis of a compensatory response on the part of the thyroid gland in an attempt to form more hormone. Of special significance in this regard is the fact that rough estimates of the comparative microscopic volume of parenchymal and lymphoid elements in struma lymphomatosa reveal that slightly more than one-half of the average gland's bulk is parenchyma. This observation seems paradoxical when the impressive degree of lymphocytic infiltration in many cases is considered, but a close study often shows the lymphocytes in intimate association with thyroid follicles in various phases of atrophy, with these acini appearing in the background in "ghost outline" form. Parmley and Hellwig,[3] as noted elsewhere in this paper, have likewise stressed the importance of the epithelial tissue in Hashimoto's struma, estimating that it contributed more than one-half of the gland's mass.

Fibrosis was not a prominent histologic observation in the review of this series of cases of Hashimoto's struma, although the majority of cases did reveal a slight to mild increase in the amount of connective tissue. This, however, was most usually on the order of an accentuation of the normal interlobular, fibrous septa, and not a replacement or sclerotic type of fibrosis.

Lymph nodes surrounding the gland were removed in nine of the adults, but in five they were described as being normal in size. In the other four they were described as being hyperplastic. In each of the three young girls, hyperplastic nodes were also found. The question arises whether the large nodes in the girls reflect the changes in the thyroid gland or are merely part of the more general lymphoid hyperplasia of childhood. Although some authors[6] have noted the absence of regional nodes, their presence in seven patients in this series is at least suggestive that lymph-node hyperplasia is not too infrequent, as McClintock and Wright[1d] have noted.

REPEAT BIOPSIES

Although nothing is definitely known about the pathogenesis of struma lymphomatosa in its incipiency, some information has been gained on the progress of the established disease from cases in which second operations were required because

6. (*a*) Joll.[2c] (*b*) Schilling, J. A.: Struma Lymphomatosa, Struma Fibrosa and Thyroiditis, Surg., Gynec. & Obst. **81**:533-549 (Nov.) 1945.

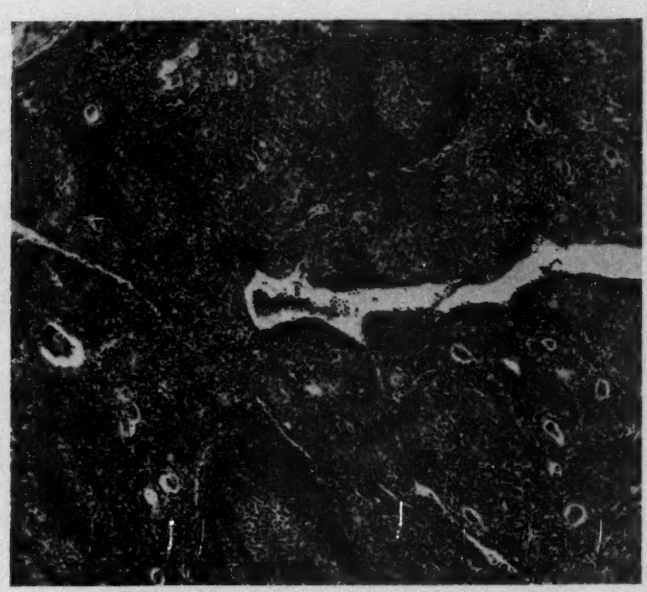

Fig. 2 (Case 8).—First biopsy specimen from a symmetrically enlarged thyroid gland with a diagnosis of struma lymphomatosa. A few atrophic follicles are visible in the "sea of lymphocytes." × 67.

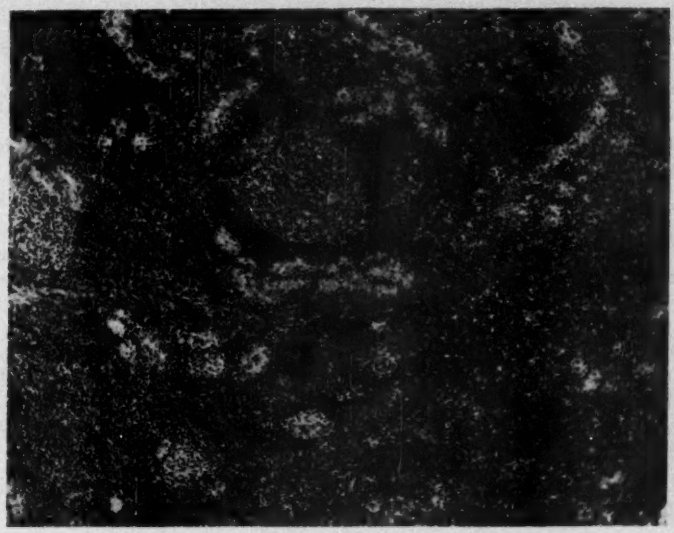

Fig. 3 (Case 8).—Another biopsy specimen taken four years later from the same gland as shown in Figure 2. The histologic similarity is apparent. × 67. The patient received thyroid medication during the four-year interim, with an associated decrease in the size of the thyroid.

of regrowth of the gland. Heyd's case,[7] after an interval of 13 mo., showed little change except possibly some increase in fibrosis. Clute and co-workers [8] reported a case showing struma lymphomatosa in sections made two years apart; however, no description is given of the microscopic observations. McClintock and Wright's case,[1d] after an interval of 13 mo., showed little change except some increase in fibrosis. Joll [2c] states that in a case of his, with reoperation after four years, there were no essential changes. Hellwig's case [9] after nine years showed no change in the microscopic picture. Schilling's first case [6b] showed no changes after 11 mo. In his second case the original slides were lost, and no comparison could be made, although the diagnosis was the same each time.

One of our patients (Case 8) had a diagnostic biopsy specimen of the right lobe of the thyroid gland, and subsequently for four years she was maintained with adequate doses of thyroid extract. At the end of this period, the gland had markedly decreased in size and clinically only a thin, cord-like pyramidal lobe was palpable. Biopsy of the latter was performed. On examination of the two biopsy specimens, no significant changes were observed in the histologic picture (Figs. 2 and 3).

SEX, AGE, AND DISTRIBUTION

In this series, as in others, the marked predilection for females is evident. All our patients were women. One patient, a man aged 67, was found to have Hashimoto's struma incidentally at postmortem study. Because of lack of clinical data relative to his thyroid status, he has not been included in the series. A few instances of struma lymphomatosa occurring in males have been reported in the literature,[10] but the incidence is low. In several of the reported cases of males, the diagnosis is questionable.

The disease is predominantly one of the fifth and sixth decades; however, age is not a specific diagnostic feature.[1d] The youngest patient, a girl 14 yr. of age, was reported on by McQuillan.[11] In our group I there are two girls (Cases 10 and 14) each aged 10 yr. and one girl (Case 6) aged 14 yr. who had been known to have a goiter since the age of 6 yr. Another patient (Case 51) had a goiter since the age of 12 yr., but the diagnosis was not established until nine years later. To our knowledge, these are the youngest reported patients. With inclusion of the three youngest patients, the average age of this series is 42.3 yr. With their exclusion, the average age is 44.2 yr., which corresponds to that given for other large series.[12] In Table 1 the cases have been broken down arbitrarily into physiologic age groups, and twice as many cases in this series occurred after 36 yr. of age as before.

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7. Heyd, C. G.: Riedel's Struma: Benign Granuloma of the Thyroid, S. Clin. North America **9**:493-513 (June) 1929.

8. Clute, H. M.; Echerson, E. B., and Warren, S.: Clinical Aspects of Struma Lymphomatosa, Arch. Surg. **31**:419-428 (Sept.) 1935.

9. Hellwig, C. A.: Lymphadenoid Goiter, Arch. Path. **25**:838-849 (June) 1938.

10. Schilling.[6b] Kearns, J. E., Jr.: Struma Lymphomatosa (Hashimoto), Ann. Surg. **112**:421-425 (Sept.) 1940.

11. McQuillan, A. S.: Thyroiditis, Tr. Am. A. Study Goiter, 1938, pp. 212-219.

12. McSwain and Moore.[2a] Patterson and Starkey.[2b] Parmley and Hellwig.[3]

Although most of the patients were natives of the New England states, they were of widely varied extractions. There has been little evidence in the literature of a significant geographical distribution. However, Joll [2c] indicated that struma lymphomatosa may be somewhat more frequent in nongoitrous districts. There were no Negro patients in this group, and the fact that few intances of the disease in the Negro race have been reported is worthy of note.

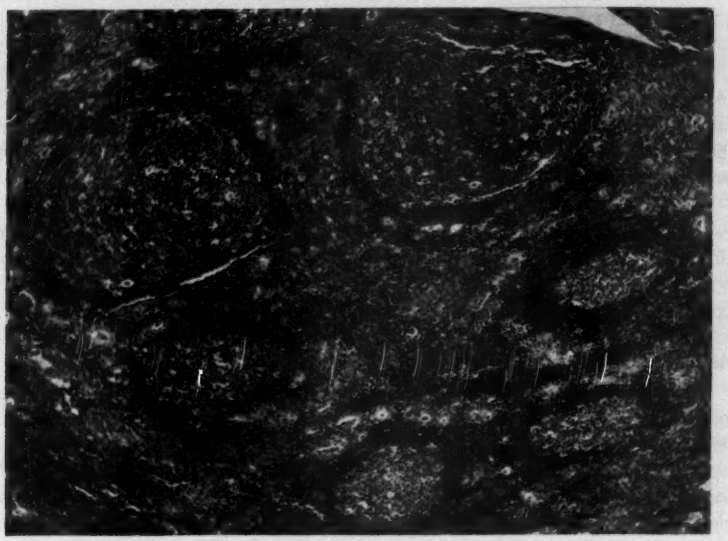

Fig. 4 (Case 10).—Struma lymphomatosa in a 10-yr.-old girl, with clinical signs of early myxedema. Degenerative thyroid acini are visible scattered about the periphery of lymphoid germinal centers. × 67.

TABLE 1.—*Cases Arranged According to Physiologic Age Groups*

0-10 Yr. Childhood	11-17 Yr. Puberty	18-35 Yr. Early Reproductive	36-53 Yr. Late Reproductive and Menopausal	54-74 Yr. Postmenopausal
2	1	14	22	12

SYMPTOMS

In all the patients except four (Cases 6, 10, 29, 48) the chief complaint was the enlargement in the neck, and a high proportion had symptoms of mild or moderate pressure, such as dysphagia, choking, cough, dyspnea, or pressure when bending or on lying down. Only five of the patients complained of mild tenderness, and this was usually in the nature of an ache. Although tenderness and pain are not frequent,[13] Patterson and Starkey [2b] noted its presence in five of 11 cases. Nervousness, fatigue, and palpitation were frequent complaints, but one cannot

13. (*a*) Joll.[2c] (*b*) Marshall and others.[2d] (*c*) Schilling.[6b] (*d*) Lee, J. G.: Chronic Non-Specific Thyroiditis, Arch. Surg. **31**:982-1012 (Dec.) 1935.

attribute these to the thyroid status, rather than to coexisting menopause, neurasthenia, or anxiety about the goiter. Schilling [6b] also felt that nervousness in these patients was not a reflection of thyroid activity. Several authors have noted the symptoms of thyrotoxicosis in "early cases." [14] Whether such cases can accurately be called struma lymphomatosa is debatable, and this point will be discussed later. Only four patients were considered to have possible early myxedema preoperatively (Cases 8, 10, 11, 35). However, cases with full-blown myxedema are not unusual and have been reported by several investigators.

Six patients had long-standing goiters, of more than five years' duration, with no evidence of recent growth (Cases 8, 16, 46, 50, 51). The time indicating the duration of goiter or change in size of a long-standing goiter, in the whole series, was less than one year in 19 patients and less than four years in 40 patients. These findings are in agreement with those of McClintock and Wright.[16d] However, others have reported longer or shorter average durations.[16]

The patients were remarkably free from other diseases. The association of previous or concomitant infections of the upper respiratory tract or other infections with the onset of the goiter was uncommon [4] and no more than one might expect in the population generally. The majority of the patients were subjected to specific questioning concerning previous symptoms of thyrotoxicosis, and in no case was such information elicited.[16] One patient (Case 18) had hypertension and had been receiving sizable doses of potassium thiocyanate for two years.

Parmley and Hellwig,[8] in discussing the endocrinologic aspects of the disease, pointed out the frequency of menstrual abnormality among their 14 cases. In the present series there were 21 patients who were still menstruating. Of these, two patients (Cases 17 and 28) had irregular menses and hot flashes, which were diagnosed as being menopausal. The remaining 19 of the 21 were entirely normal with respect to the menses. We can find no correlation with changes in menstrual cycle, except for the somewhat higher incidence of the disease in the menopausal age group.

PHYSICAL FINDINGS

The physical findings are almost entirely those associated with the neck enlargement and hypometabolism, or hypothyroidism if present. The only significant clinical finding is the firmness of the gland. It is rarely hard and never as hard as the typical Riedel's struma. The boundaries are ordinarily clearly defined. The surface may feel lobulated, and not uncommonly the lobulations become greatly enlarged and have been described as "pseudopodia." [17] The term "nodular" has often been used to describe a gland which was actually lobulated on the surface.

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14. (*a*) Vaux.[1a] (*b*) Lee and McGrath.[1b] (*c*) Patterson and Starkey.[2h] (*d*) Clute and others.[8] (*e*) Bothe, F. A.: Riedel's Struma and Struma Lymphomatosa, Clinics **3**:215-220 (June) 1944. (*f*) Polowe, D.: Struma Lymphomatosa (Hashimoto) Associated with Hyperthyroidism, Arch. Surg. **29**:768-777 (Nov.) 1934. (*g*) Boyden, A. M.; Coller, F. A., and Bugher, J. C.: Riedel's Struma, West. J. Surg. **43**:547-563 (Oct.) 1935.

15. Patterson and Starkey.[2b] Marshall and others.[2d] Schilling.[6b]

16. (*a*) Joll.[2e] (*b*) Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid: Struma Lymphomatosa (Hashimoto), Arch. Surg. **22**:548-567 (April) 1931.

17. Means, J. H.: Thyroid and Its Diseases, ed. 2, Philadelphia, J. B. Lippincott Company, 1948, p. 480.

The goiter is usually symmetrical; however, frequently there may be more swelling on one side than on the other.[18] If the disparity between the lobes is great, the gland may give the impression clinically of being a single, large, unilateral nodule. The size of the gland varies from little larger than normal to nearly 10 times normal. In this series regional lymph nodes were not frequently palpated, having been noted as clinically present in only three cases.

STUDIES INCLUDING RADIOACTIVE-IODINE-TRACER OBSERVATIONS

It has been reported that the routine laboratory tests have no special characteristic results in struma lymphomatosa,[2a] and we have found this to be true. As a possible indication of adrenal-cortical function, the eosinophil percentages of total white blood cell counts were within normal limits. Studies of eosinophil response to corticotropin (ACTH) or epinephrine (adrenalin®) were not done.

Blood cholesterol levels ranged from 141 to 326 mg. per 100 cc. Basal metabolic rate determinations were done at least twice for most of the patients. The rates ranged from +16 to —33% and averaged —8.3%. One patient (Case 43) with a basal metabolic rate of +16% was clinically euthyroid. However, this case was included in Group II because of the question of mild thyrotoxicosis. Protein-bound-iodine (PBI) studies were done on three patients. In one patient (Case 8) the result was 2.5 γ per 100 cc. In another (Case 10) it was 0.9 γ per 100 cc., and in a third patient (Case 6) the result was 4.4 γ per 100 cc. In the second patient (Case 10) the level was in definite myxedema range, while values in the other two were indicative of hypothyroidism.

Tracer doses of radioactive iodine (100 μc of I^{131} with 100 γ of sodium iodide as carrier) were given to seven patients, and the urinary excretion of radioactive iodine was determined for the subsequent 48-hr. period. From this, the uptake of I^{131} by the thyroid was computed, with the following results:

Case No.	I^{131} Uptake by Thyroid, %
6	27.7
13	38.0
15	40.6
18	34.0
29	15.6
36	21.6
46	58.0

Except for Case 29, these could all be considered as within normal range, since there is ordinarily a wide overlap in the uptake in the hyperthyroid, hypothyroid, and euthyroid categories. In Case 29 there was no myxedema in spite of the low uptake of I^{131} by the thyroid gland, and we cannot explain this low result. The average uptake of I^{131} by the thyroid was 33.6%, which is in the lower range of normal.

RADIOAUTOGRAPHS

A study of the radioautographs of histologic preparations in three patients (Cases 6, 15, 20) who had received a tracer dose of 500 μc of radioactive iodine (I^{131}) the day prior to thyroidectomy disclosed some of the usual disconcerting

18. (*a*) Joll.[2c] (*b*) Crile, G., Jr.: Thyroiditis, Ann. Surg. **127**:640-654 (April) 1948.

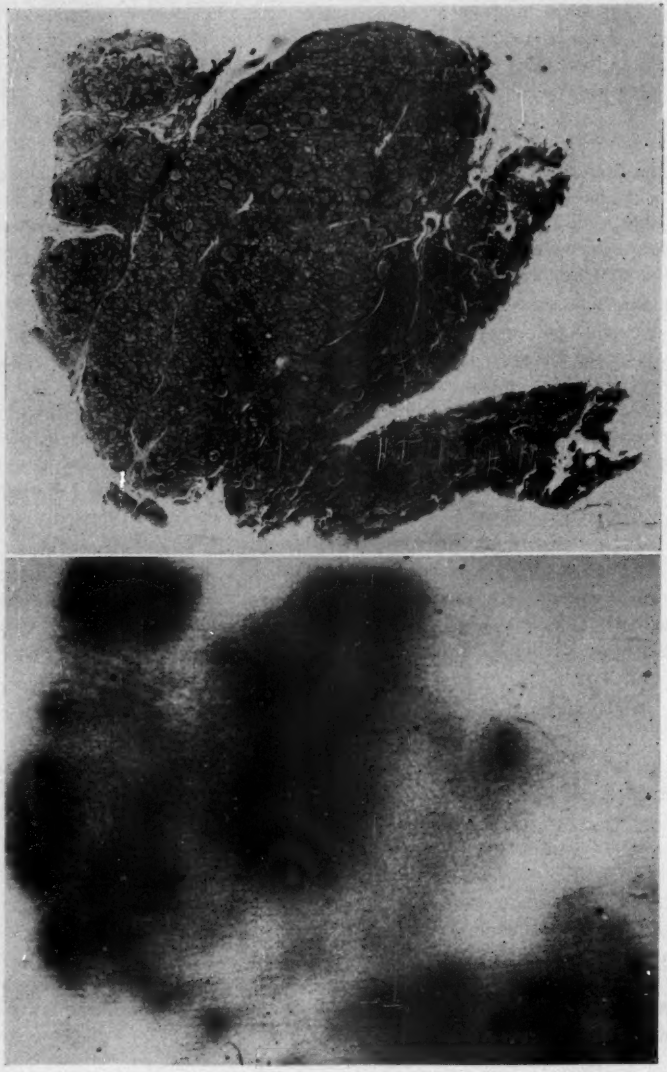

Fig. 5 (Case 20).—Low-power photomicrograph (upper) and radioautograph (lower) from a patient with typical Hashimoto's struma who had been given a tracer dose of radioactive iodine preoperatively. The small circular islands in the photomicrograph are germinal centers of lymphoid follicles. Although the section shows a diffuse infiltration with lymphoid tissue and considerable parenchymal atrophy, nearly all areas still reveal some evidence of function as indicated by the general darkening of the radioautograph. × 7.5.

features encountered in attempts to correlate thyroid histologic changes with areas of radioactive-iodine uptake, namely, that of the difficulties in predicting the radioactive-iodine uptake in a specific area from a study of the histologic appearance and vice versa. Areas largely composed of lymphocytes with only the bare outlines of residual thyroid cells could not naturally be expected to show any demonstrable uptake of radioactive iodine, and such was the case. However, other zones composed primarily of degenerating follicles sometimes showed a small amount of darkening of the radioautograph film where, from the histologic appearance alone, one would suppose that the seeming degree of atrophy would preclude any functional activity (Fig. 5). This observation might possibly help to explain the relatively low incidence of frank myxedema in patients with struma lymphomatosa in whom the histologic picture alone would indicate a profound diminution in gland function and depression in hormone output. A similar study of this type in one case was recently reported by Dempsey and others,[19] who found no radioactivity in zones of acidophilic epithelium and scattered foci of radioactivity in zones with follicles formed by neutrophilic, cuboidal epithelial cells.

DIFFERENTIAL DIAGNOSIS

Diagnosis cannot be made with certainty from clinical findings alone; however, it can be suspected. In this series, the clinical diagnosis of chronic thyroiditis was seriously considered in 18 instances, and of these Hashimoto's struma was suspected five times. The condition most frequently confused clinically with struma lymphomatosa was nodular colloid goiter, and this diagnosis was made 25 times. When marked asymmetry was present, giving the clinical impression of a single firm adenoma, carcinoma was suspected, and this diagnosis was made in six instances. Adenoma was diagnosed three times.

THERAPY

Thirty-six patients in this series and most patients reported on in the literature have had subtotal thyroidectomies. When the process was asymmetrical, hemithyroidectomies have been done, and such procedures were performed here. In recent years, removal of the isthmus for decompression of the trachea has been recommended,[2c] and this may be followed by irradiation therapy to the remaining tissue. Five such decompressions were done in the present series. Although Crile [18b] recommends conservative surgical measures, Marshall and co-authors [2d] believe little is to be gained by sparing tissue as far as development of symptoms is concerned, since hypothyroidism develops in a high percentage of patients regardless of the amount of tissue spared. Sufficient removal of thyroid tissue to prevent pressure symptoms appears to be the prime requisite.[17]

Several writers [20] feel that irradiation is the treatment of choice after diagnosis on biopsy. Schilling [6b] uses 1,200 to 1,500 r of roentgen radiation in divided doses and has found that the gland shrinks in weeks to two months. However, others [21] do not favor irradiation because of possible increase in fibrosis locally with aggravation of pressure symptom.

19. Dempsey, W. S.; Dinsmore, R. S., and Hazard, J. B.: Struma Lymphomatosa, Cleveland Clin. Quart. **16**:132-135 (July) 1949.

20. Schilling.[6b] Crile, G., Jr.: Treatment of Thyroiditis, Arch. Surg. **57**:443 (Oct.) 1948.

21. Marshall and others.[2d] Boyden and others.[14g]

In the present series, adequate follow-up observations were available in four patients treated by irradiation. One patient (Case 1) received 1,200 r to the left lobe after right hemithyroidectomy, and in three months the lobe was no longer palpable. Another (Case 24) received 1,200 r after a recurrence of the goiter, and within two months the gland was smaller. At the end of a year, it was almost gone. A third patient (Case 41) had recurrence on the right side of the neck 14 mo. postoperatively. She was treated with 900 r, and six months later the right lobe was two times normal size. The last patient (Case 44) was given 800 r to the left lobe two and a half years following right hemithyroidectomy, and nine and a half months later the gland had not changed. It appears from these results that 1,200 r produces a marked regression in the size of the thyroid gland.

FOLLOW-UP STUDIES

The possibility of a relationship between struma lymphomatosa and lymphosarcoma has been suggested,[22] but there was no interpretable evidence in our data to indicate any such relationship.

With exclusion of the rare postoperative complications, the end result of surgical treatment or irradiation is myxedema in a high proportion of the cases. Although earlier writers set this figure at 40%, more recent reports give an incidence of about 80%.[23] Adequate follow-up reports were available on 29 patients in this series. Twenty-four of the 29 patients eventually received thyroid, although in most of them this medication was started before the full-blown picture of myxedema appeared. The dose of thyroid varied from 65 to 130 mg. daily and was usually determined by the clinical state of the patient, even though basal-metabolic-rate estimations were often low.

Among the many cases reported in the literature, numerous instances of regrowth of the thyroid have been recorded, and in a number of these reoperation was required. Nowhere has there been any definite observation on the possible cause of this regrowth of the goiter. Ficarra [24] believes it is due to inadequate surgical removal. This seems unlikely in view of recurrences despite bilateral subtotal thyroidectomies with removal of all but a small fraction of the gland mass. Schilling [6b] states that the fact that so few have second operations is ample evidence that the process becomes stationary. It is difficult to accept this as entirely satisfactory evidence without knowing what other therapy was given postoperatively.

Listed in Table 2 are the instances in this series of regrowth of goiter as related to the postoperative administration of thyroid, excluding those patients in whom irradiation therapy obscured the course.

Of the seven patients showing regrowth of thyroid tissue postoperatively in Table 2, Group A, four are of special interest. One (Case 16) had subtotal thyroidectomy, leaving an estimated 4 to 5 gm. of tissue on each side. During the ensuing two and a half years, this patient took thyroid for only two four-month periods, and the gland gradually enlarged to two times normal size. The second

22. Graham, A.: Riedel's Struma in Contrast to Struma Lymphomatosa (Hashimoto), Tr. Am. A. Study Goiter, 1931, pp. 3-11.

23. Lee and McGrath.[1b] McClintock and Wright.[1d] Graham.[4] Lee[13d] Graham.[22]

24. Ficarra, B. J.: Struma Lymphomatosa (Hashimoto): Clinicopathologic Study, Arch. Surg. **52**:729-736 (June) 1946.

patient (Case 24) had a subtotal excision, leaving an estimated 5 gm. on the right and 7 gm. on the left side. During the next seven months, while she received no thyroid therapy, the gland regrew to one to two times normal, and a course of irradiation therapy was then given. The third patient (Case 25) had a subtotal resection, leaving a "slight amount" of tissue on each side of the trachea. In 17 mo. the gland regrew, so that it could be palpated on both sides. The patient was subsequently seen irregularly, and 14 yr. postoperatively the gland was one and one-half times normal size, in addition to being firm and nodular. The fourth patient (Case 41) had subtotal thyroidectomy, leaving 5 to 10 gm. of tissue on the right side and 5 gm. on the left. In 14 mo. the right lobe was about two times normal size, and thereupon this patient was given irradiation treatment. The other patients showed unqestionable enlargement, but of less striking degree.

TABLE 2.—*Postoperative Regrowth of Thyroid Tissue as Related to Administration of Thyroid* *

		Case No.
Group A: Postoperatively little or no thyroid administered		
No regrowth or change in size of thyroid gland		7
		43
	Total, 3 cases	53
Regrowth or increase in thyroid size		1
		14
		16
		24
		25
		26
Total Group A, 10 cases	Total, 7 cases	41
Group B: Postoperatively adequate doses of thyroid administered		
No regrowth of thyroid tissue		2
		3
		4
		6
		8
		10
		11
		14
		23
		29
		35
		36
		46
	Total, 14 cases	48

* Several cases of Group A are also included in Group B, since the patients subsequently received adequate doses of thyroid (see text).

In Table 2, Group B, seven patients are of special interest. The first (Case 8) had a biopsy of the right lobe and was subsequently given thyroid regularly. Upon examination four years later, the gland was not palpable at all. The pyramidal lobe, which had been described originally as being "impressively enlarged" by Dr. J. H. Means, was found to be a thin, barely palpable cord. In the second patient (Case 10) the isthmus and the anterior third of each lobe were removed. Postoperatively, the gland was palpable and thyroid was given regularly. In one and one-half years the gland could not be felt. The third patient (Case 4) had subtotal thyroidectomy, and a considerable amount of tissue (approximately 20 gm.) was left on each side. Seven months postoperatively the gland was palpable bilaterally. Thyroid was then administered, and seven months later the gland was not felt. The next patient (Case 12) had a right hemithyroidectomy and then received thyroid. In the course of three years the remaining tissue decreased from about three times normal to little larger than normal. Six years postoperatively, with administration of thyroid and also of potassium thiocyanate for hypertension, the gland was slightly larger than normal. The fifth patient (Case 2) had subtotal excision, leaving more tissue on the right

side than on the left. Thyroid was taken irregularly for two years and then apparently regularly for the next year. During this time the gland grew to three times normal size. Thyroid therapy was then continued regularly, and in the course of the next six years the gland became impalpable. The sixth patient (Case 46) had right hemithyroidectomy, and three and a half months postoperatively a "moderate amount" of tissue was felt bilaterally. In the next two and a half years the patient claimed having taken thyroid for one year, but not at all for the last year and a half. The left lobe was one and one-half times normal size. She then received thyroid regularly, and four months later the gland was questionably palpable. In the last patient (Case 36) the changes were much less striking, yet the gland, which was not felt after the operation, became palpable one and a half years later while thyroid was not being taken. However, while she was receiving thyroid, it became impalpable. When thyroid therapy was discontinued, the gland was again felt. Similarly suggestive are Cases 39, 44, and 41, which were described in the section on irradiation therapy.

Thus, in 15 cases adequate doses of thyroid alone prevented the regrowth of the goiter postoperatively, and when regrowth of the goiter occurred on discontinuation of thyroid therapy there was regression in the gland size on the readministration of adequate doses of thyroid. In seven cases this effect of thyroid seemed to be quite striking. This observation is of considerable interest and will be discussed later. Probably larger doses of thyroid could have been given in the present series, as hypometabolism was still present in many instances, and perhaps more decided effect on gland size might have occurred. It appears that 100 to 130 mg. of thyroid U. S. P. per day is an adequate dose in most cases.

It is quite conceivable that in a goiter of many years' duration adequate doses of thyroid might not initiate any regression in gland size.

In the literature one can find a number of examples in which administration of thyroid seemed to cause a regression in the gland size. Conversely, one can find many instances in which the thyroid gland apparently regrew while the patient was receiving thyroid. However, as follow-up data were not recorded from the standpoint of the effect on the gland of thyroid administration, the information is not clear, and it is probably wrong to draw conclusions from such data.

COMMENT

As Graham and others have repeatedly indicated, the individual changes that make up the histologic picture of struma lymphomatosa are in no way characteristic for this disease alone. Similar histologic changes in various degrees of combination are found in the goiter of Graves's disease (toxic diffuse goiter), colloid goiter, adenomatous goiter, Riedel's struma, and the shrunken atrophic thyroid of primary myxedema. Therefore, if histologic evidence is used as the only basis for diagnosis, confusion will arise in the borderline cases, in which the character and proportions of the above-mentioned histologic changes overlap. If, however, the clinical picture is taken into consideration, one finds generally, as described above, that these patients are women in the fourth or fifth decade of life, and that usually there has developed in less than four years a diffuse firm goiter without clear-cut relationship to infection, thyrotoxicosis, or other obvious cause for the disease. This clinical

picture, added to the required gross and microscopic evidence, is necessary for the diagnosis of the clinicopathologic entity of struma lymphomatosa.

Good résumés of the various etiological theories have been published.[25] Infection has been advanced as a possible cause of struma lymphomatosa,[26] and the evidence has been well summarized.[27] This idea, however, has been largely discarded by most recent students of the disease. We are in accord with this view, as the present series discloses the apparent absence of infiltration of surrounding tissue, lack of fever, local pain and tenderness, and leucocytosis, and absence of a history of infection. Several authors have attributed the picture of struma lymphomatosa to prolonged iodine administration.[14g] The lack of a relationship between struma lymphomatosa and prolonged iodine administration in the present series seems to make such a hypothesis untenable. Most authors are in agreement with the latter view. Vitamin deficiency has also been suggested by the experimental work of McCarrison,[28] who apparently produced the morphologic changes of struma lymphomatosa in 25% of rats maintained on a strict vitamin-deficient diet. Although it was not possible to go into the dietary details of most of the patients in this series, there did not seem to be clinical or laboratory evidence suggestive of any of the known vitamin-deficiency diseases.

The possible relationship to the adrenal glands is suggested by the reports of cases in which similar pathologic changes were observed at autopsy in both the thyroid and the adrenal glands, yet the changes in each of these glands may occur independently of the other.

Simple atrophy does not seem to account for the changes seen in the thyroid gland of struma lymphomatosa, as substantiated by evidence derived from the examinations of the thyroid glands from patients with panhypopituitarism which were done in this hospital (Fig. 6).

The limitation of the disease to women, with predilection for the menopausal period, would seem to point to an ovarian-hormone-lack relationship. Hellwig [9] stated that the disease is probably a result of overstimulation of the gland with pituitary thyrotropin (thyroid-stimulating hormone). Later [8] he modified this view with the idea that cessation of ovarian function, by causing pituitary overactivity with respect to follicle-stimulating hormone (F. S. H.), might concomitantly produce an excess of thyroid-stimulating hormone as well and, therefore, produce the changes noted in struma lymphomatosa. This concept, however, does not explain why a significant number of cases are seen in normally menstruating women.

Many writers have remarked on the histologic similarity of the goiters in struma lymphomatosa and toxic diffuse goiter. The idea has been expressed that struma lymphomatosa occurs in persons with the "Graves constitution of Warthin,"[14g] but in whom the pathologic process takes an unusual course, or in whom exhaustion is a result of overstimulation.[9] Histologically, this concept is an attractive one, because of the large amounts of lymphoid elements often seen in the hyperplastic

25. Womack.[1c] Joll.[2c] Schilling.[6b]

26. Shaw, A. F. B., and Smith, R. P.: Riedel's Chronic Thyroiditis with a Report of 6 Cases and a Contribution to the Pathology, Brit. J. Surg. **13**:93-108 (July) 1925.

27. Schilling.[6b] Boyden and others.[14g]

28. McCarrison, R.: Note on the Experimental Production of Lymphadenoid Goiter in Rats, Brit. M. J. **1**:5 (Jan. 5) 1929.

glands of toxic diffuse goiter. It is only one step further to conceive of some such overworked glands lapsing finally into a "burnt-out" stage, with the thyroid cells exhibiting signs of degeneration. Graham and McCullagh [16b] once stated that if patients with Hashimoto's struma had a background of hyperthyroidism there would be a logical explanation for the source of the disease. Vaux [1a] states that seven of her 13 patients with the "early" disease showed evidence of thyrotoxicosis. Joll,[2c] however, did not regard these cases as true instances of struma lymphomatosa. The presence of focal areas of parenchymal hyperplasia in Hashimoto's struma has often been used as an argument indicating a relationship of the two diseases. However, such hyperplastic foci seem more logically explained on a basis of compensatory hyperplasia secondary to extensive parenchymal degeneration. The absence of clinical or laboratory evidence of thyrotoxicosis supports the latter

Fig. 6.—Thyroid from a patient with panhypopituitarism (MGH 67955). The replacement fibrosis and only scattered small islands of remaining follicles are typical changes in the thyroid atrophy of Simmonds' disease. × 50.

interpretation. In toxic diffuse goiter some glands show foci of epithelial degenerative changes similar to those always seen in struma lymphomatosa, and lymphocytic infiltration, with lymph-follicle formation, may be a prominent feature. For these various reasons several authors have been led to postulate that, although struma lymphomatosa is not a result of toxic diffuse goiter, it is due to the same mechanism, namely, overstimulation with pituitary thyroid-stimulating hormone.[9] It has been suggested by Schilling [6b] that the excessive functional demands on the thyroid in the female in connection with puberty, menstruation, pregnancy, and menopause may be the cause of degenerative changes in the gland. Williamson and Pearse [29]

29. Williamson, G. S., and Pearse, I. H.: Lymphadenoid Goiter and Its Clinical Significance. Brit. M. J. **1**:4-5 (Jan. 5) 1929.

believed the cause to be a physiologically subnormal gland with compensatory lymphocytic hyperplasia owing to failure of the usual hyperplastic efforts of the epithelium.

The experiments of Turley and Richter [30] are of interest in regard to the possible relationship of toxic diffuse goiter and struma lymphomatosa. They administered a lymphocytogenic drug, "aleuronat," an albuminoid substance derived from wheat starch, along with lethal doses of thyroxin to guinea pigs and thus prevented death from thyrotoxicosis, which ordinarily would have occurred in two to five days if thyroxin had been administered alone. The question arises whether the lymphocytic infiltration in toxic diffuse goiter is a defense mechanism to abate the thyrotoxicosis. Rawson's experiments,[31] in which it was shown that lymphoid tissue inactivates thyroid-stimulating hormone, might indicate that the lymphocytic hyperplasia is a reaction on the part of the body to inactivate thyroid-stimulating hormone. A number of cases of Addison's disease have been reported associated with marked lymphocytic infiltration of the thyroid, and in two of these, in which examination of the hypophysis was recorded,[32] there was hypertrophy of the pituitary eosinophil cells (from which thyroid-stimulating hormone is believed to originate).[33] Ferguson,[34] however, suggested that the hydrolysis of lipids contained in the colloid might initiate the tissue reaction when thyroid follicles were disintegrating.

From the study of the present series of cases, certain things have been learned which may help to answer some of the questions. If one assumes that an excess of thyroid-stimulating hormone occurs primarily and that all the thyroid epithelial cells are normal prior to this excess, one would expect to find, at least in "early cases," unequivocal clinical and laboratory evidence of increased thyroid activity, such as is found in toxic diffuse goiter. However, this was not found to be so. Clinically, these patients were hypometabolic, with normal or slightly decreased basal metabolic rates, and apparently there was a diminished capacity for thyroid-hormone formation, as confirmed by the lowered serum protein-bound-iodine levels, low normal I^{131} uptake by the thyroid gland, and the radioautographs indicating the epithelial cells to be less avid for I^{131}. Therefore, the fault would seem to lie initially at the thyroid cell level, and excess of thyroid-stimulating hormone presumably follows as a result of diminished thyroid-hormone formation.

Hellwig reported that the average partition of epithelium to lymphoid tissue in struma lymphomatosa is about 60:40. Since the volume of the gland may be increased two or more times, the total epithelial surface would seem to be adequate for maintaining an almost normal or slightly reduced basal metabolic rate, even though thyroid-cell function is somewhat depressed. However, it seems that with

30. Turley, L. A., and Richter, K. M.: Experimental Study of the Lymphocytic Response in Thyrotoxicosis, J. Lab. & Clin. Med. **27**:1-11 (Oct.) 1941.

31. Rawson, R. W.; Sterne, G. D., and Aub, J. C.: Physiological Reactions of the Thyroid-Stimulating Hormone of the Pituitary, Endocrinology **30**:240-245 (Feb.) 1942.

32. Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Suprarenals, Quart. J. Med. **22**:121-144 (Oct.) 1928.

33. Albright, F., and Elrick, H.: Attempt to Classify Hormonal Disorders of the Hypophysis, Tr. A. Am. Physicians **61**:42-53, 1948.

34. Ferguson, J. A.: Tissue Reaction to Colloid and Lipoids from the Human Thyroid Gland, Arch. Path. **15**:244-254 (Feb.) 1933.

the progress of epithelial degeneration the thyroid-hormone output is further decreased. This, in turn, presumably stimulates the pituitary to produce more thyroid-stimulating hormone. The latter probably causes further increase in thyroid-gland size and probably stimulates residual normal thyroid epithelial cells, if present, to become hyperplastic. This might account for the islands of hyperplasia one sees in some cases of Hashimoto's struma. In addition, from the present study, it is apparent that in cases in which the thyroid gland was increasing in size after the operation the administration of thyroid alone in adequate doses stopped this regrowth of tissue and caused a marked diminution or clinical disappearance of the gland without essential change of the pathological features (Case 8, in which a second biopsy was made). This also appears to confirm the fact that increase of thyroid-stimulating hormone is a secondary phenomenon and that thyroid-cell failure is the primary event, if we accept the present concept that thyroid-stimulating hormone and thyroid hormone are reciprocally related, and that with increase of thyroid hormone there is a decrease of thyroid-stimulating hormone and vice versa.[35]

It seems most likely, therefore, from an analysis of the data on this series that there are initial changes in the thyroid cells whereby their capacity to produce thyroid hormone is diminished. The cause or causes of this primary alteration in the status of the thyroid cell is not apparent from this study. It would seem that the thyroid epithelial change is a slow, gradual process and has a tendency to become diffuse, yet it does not completely alter the specific function of the thyroid cells. It diminishes their functional capacity but does not destroy the functional capacity completely, or at once, or to a uniform degree in all cells. This alteration seems to have a predilection for women in the menopausal age group. That ovarian-hormone lack enhances the process is difficult to prove in view of the patients with a normal menstrual history, as previously stated. We are left, therefore, with altered thyroid cells with diminished functional capacity of unknown causation. It remains for future study to elucidate the cause or causes of this change. It may be an intrinsic primary change of an intracellular enzyme mechanism arising *de novo*, or the result of some hormone lack, hormone excess, or some mild exogenous or endogenous toxic agent or agents. It is quite conceivable, therefore, that the picture of struma lymphomatosa may have varied etiological agents, the common denominator of which is a slow degeneration of thyroid epithelial cells, with the same metabolic alteration of the cells of a diffuse nature without actual and uniform destruction of parenchymal cells.

Whatever the etiological agent is that initiates epithelial degeneration in struma lymphomatosa, it is not of the same nature as the blocking agents (i. e., thiourea derivatives). Thiourea derivatives probably produce blocking of an enzyme mechanism necessary for normal thyroid-hormone synthesis and thereby cause a thyroid-hormone deficiency with compensatory excess of thyroid-stimulating hor-

35. Salter, W. T.: Endocrine Function of Iodine, Cambridge, Mass., Harvard University Press, 1940. Marine, D.: The Pathogenesis and Prevention of Simple or Endemic Goiter, J. A. M. A. **104**:2334-2341 (June 29) 1935. Means, J. H.: Diseases of the Thyroid Gland, New England J. Med. **221**:820-825 (Nov. 23) 1939. Uotila, U. U.: The Regulation of Thyrotropic Function by Thyroxin After Pituitary Stalk Section, Endocrinology **26**:129-135 (Jan.) 1940.

mone, yet the thyroid cells are quite capable of undergoing uniform hyperplasia simulating the hyperplasia of toxic diffuse goiter. In struma lymphomatosa, on the other hand, there does not appear to be a comparable blocking of an enzyme system of this type. It would seem to be an over-all depression of the whole cell mechanism of thyroid-hormone synthesis, as these cells are still capable of producing apparently normal thyroid hormone, although in reduced amounts and at a reduced rate; but, owing probably to some degenerative change in the epithelial cells, they are apparently incapable of responding to increased thyroid-stimulating hormone with the same degree of hyperplasia that is found with the blocking agents.

From the above speculations, one may ask: If the fault lies within the thyroid cell and consists of a process of varying degrees of degeneration and loss of function, what relation may this have to so-called primary myxedema, in which for some unknown reason essentially all the thyroid cells cease functioning and atrophy? We should like to submit the suggestion that perhaps struma lymphomatosa represents a "forme fruste" of primary myxedema. The damaging agent (or agents, or defect of intracellular enzyme mechanism, etc.) does not produce complete degeneration of epithelium as it probably does in primary myxedema, and only a portion of the total number of cells degenerate. Although many of the cells are damaged, they are not destroyed. It is the latter fact that would enable subsequent stimulation of thyroid-stimulating hormone (in response to diminished thyroid hormone) to cause gradual enlargement and goiter formation. In such a hypothesis the other pathologic changes would be subsequent to the initial epithelial-cell degeneration rather than concomitant with it. Such a mechanism might be supported by the reported observations at autopsies in primary myxedema, in which the thyroid gland often shows microscopic pictures identical with that of struma lymphomatosa.[17] It might explain also why so-called "burnt-out Graves' disease," in which a large proportion of the cells are "exhausted" and degenerative, may end up with a picture similar to that of struma lymphomatosa, having been reported as such in the literature. The damaging agent in this instance probably is over-stimulation from thyroid-stimulating hormone itself. It would not be difficult to understand why the frequent course of Hashimoto's struma after surgical intervention is myxedema, whereas this is not true of Riedel's struma, in which the remaining cells are apparently undamaged.

The lymphoid-tissue reaction in the goiters of struma lymphomatosa seems in some way to be related to an increased effect of thyroid-stimulating hormone, and it is seen in several conditions, the common denominator of which theoretically is increased thyroid-stimulating hormone. Thus, thyrotoxicosis, primary myxedema, and colloid goiter should, according to present concepts, all have increased thyroid-stimulating hormone. Rawson's experiments,[21] as well as the instances of lymphoid hyperplasia associated with hypertrophy of pituitary eosinophil cells in cases of Addison's disease,[22] have been cited previously.

The above concepts throw no light upon the primary causation of this condition. However, if subsequent work substantiates these concepts, it would at least help to establish the relationship of this entity to other thyroid diseases and indicate the mechanism by which a similar histologic picture is produced in a wide variety of apparently unrelated thyroid diseases.

SUMMARY

Struma lymphomatosa is primarily a disease of women, occurring largely in the menopausal age group. The development of a rubbery-firm goiter in a period of usually less than four years, accompanied with symptoms of moderate pressure and moderate hypothyroidism, but unassociated with previous infection, thyrotoxicosis, or other known cause for goiter, should cause suspicion of the disease.

Diagnosis is made when the clinical syndrome is combined with the pathologic picture of thyroid cellular degeneration, diffuse lymphocytic infiltration with lymph-follicle formation, and, occasionally, slight increase in fibrous tissue.

The present study suggests that thyroid-cell degeneration is the primary event in the pathogenesis of this disease. The cause of the parenchymal degeneration is not apparent from this study.

Treatment of the patients in this series consisted of either subtotal thyroidectomy or removal of a biopsy specimen, followed by x-ray therapy. In addition, there is suggestive evidence to indicate that thyroid in adequate doses may cause regression in the size of the goiter or prevent regrowth after subtotal thyroidectomy, without necessarily altering the pathologic picture.

A hypothesis is offered as a possible explanation of the relation of struma lymphomatosa to other thyroid diseases in which nearly identical pathologic features may be present.

Dr. B. M. Dobyns permitted use of the radioautographs. Members of the staff gave permission for use of private case records.

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Case Reports

SALMONELLA ENDOCARDITIS

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BACTERIAL endocarditis caused by organisms of the Salmonella group is rare.[1] Salmonella sp. (Type Oranienburg), since its isolation by Kauffmann in 1930,[2] has never been identified as an etiological agent of endocarditis. We are, therefore, recording a case in which repeated pure blood cultures of this particular organism were obtained.

REPORT OF A CASE [3]

History.—G. A. S., a 44-yr.-old white housewife, was admitted to the medical service of Charlotte Memorial Hospital, on Sept. 18, 1950, with the chief complaint of chills and fever of 10 hours' duration.

Her past history was significant only in that at the age of 18 she was informed that she had rheumatic heart disease and at the age of 39 required hospitalization for cardiac decompensation.

She stated that two weeks prior to her admission and shortly after returning from a visit to a nearby beach resort she had a nonproductive cough, chills, fever, and general malaise. There was no associated hemoptysis, nausea, vomiting, diarrhea, or melena. Except for the cough and general malaise which persisted, she felt as though she had recovered from this episode. On the morning of admission, however, she had a shaking chill with an elevation in temperature to 38.5 C. (102 F.). Her attending physician advised hospitalization.

Results of Physical Examination.—On admission the patient had a temperature of 37.6 C. (99.7 F.), a pulse rate of 90, a respiratory rate of 24, and a blood-pressure reading of 70 systolic and 40 diastolic in the left arm and 85 systolic and 45 diastolic in the right arm. She was a well-developed, well-nourished, pale white woman, appearing chronically ill. Pertinent findings were limited to the chest and abdomen. Examination of the lungs by percussion and auscultation disclosed nothing abnormal. The heart was enlarged to the left, with the point of maximal impulse visible and palpable in the sixth left interspace at the midaxillary line. A systolic thrill was palpable over this point. There were in this same area a harsh systolic murmur transmitted into the left axilla and a late, low-pitched, diastolic murmur which was not transmitted. Along the left sternal margin a faint diastolic murmur was heard without a systolic component. No thrill was palpable over the base of the heart. The apical rate was 90 per minute; with a totally irregular rhythm. Examination of the abdomen revealed the spleen to be palpable 6 cm. below the left costal margin in the midclavicular line. There was no distention of the neck veins, ascites, or pitting ankle edema. Petechiae and ungual clubbing were not demonstrated.

From the Departments of Medicine and Pathology, Charlotte Memorial Hospital, Charlotte, N. C.

1. Jones, M.: Subacute Bacterial Endocarditis of Non-Streptococcic Etiology, Am. Heart J. **40**:106 (July) 1950.

2. Kauffmann, F.: Neue serologische Typen der Paratyphusgruppe, Ztschr. Hyg. **111**:221, 1930.

3. Dr. Luther W. Kelly, of Charlotte, N. C., permitted us to report this case.

Laboratory Findings on Admission.—Initial studies revealed an erythrocyte count of 4,100,000, with 12 gm. per 100 cc. of hemoglobin, and a white-blood-cell count of 17,000, with 97% neutrophils. Urinalysis disclosed the voided specimen to have a specific gravity of 1.023 and a 3+ reaction for albumin. An occasional white cell per high-power field was noted, but no red cells or casts were demonstrated by microscopic examination. A routine chest roentgenogram was interpreted as showing enlargement of the heart both to the right and to the left of the sternum, with prominent lung markings radiating from the hilum.

Hospital Course.—A blood culture was obtained on admission, and penicillin procaine therapy was begun. Throughout the first five days of hospitalization a total of 3,000,000 units of penicillin was administered without evidence of clinical improvement. Penicillin was then replaced by aureomycin, and in the ensuing four days a total dosage of 5.5 gm. of this antibiotic was given. On the seventh hospital day the initial blood culture was reported as yielding a pure growth of a motile Gram-negative bacillus with the cultural and morphologic characteristics of Salmonella, type unidentified. Agglutination of the organism with the patient's serum was positive in a dilution of 1:1,280. A blood culture taken on the fifth hospital day also revealed the same organism, now identified at the New York Salmonella Center, Beth Israel Hospital, New York, as Salmonella sp. (Type Oranienburg). The patient's condition did not improve, and on the eighth day of hospitalization aureomycin therapy was discontinued. Three grams of chloramphenicol (chloromycetin®) and 1 gm. of dihydrostreptomycin were then given daily for the following 10 days, during which period the patient received a total of 31.5 gm. of chloramphenicol and 13 gm. of dihydrostreptomycin. Although three blood cultures obtained during chloramphenicol and dihydrostreptomycin therapy failed to grow this bacillus, no temperature changes were noted and evidence of clinical improvement was lacking. It was decided at this time to interrupt all therapy, following which, for three days, the temperature range was within normal limits. On the fourth day after cessation of the combined chloramphenicol and dihydrostreptomycin therapy, there was a spike in temperature to 39 C. (102.2 F.). A blood culture taken at this time revealed Salmonella sp. (Type Oranienburg). Aureomycin therapy was reinstituted, and in the nine days that it was administered, the patient received a total of 15.1 gm. On the 28th hospital day, during the second trial of aureomycin therapy, antibiotic sensitivity tests were performed.[4] These in vitro studies indicated that chloramphenicol produced marked inhibition of growth, while terramycin, dihydrostreptomycin, and streptomycin, respectively, were found to be less effective. Penicillin and bacitracin produced no inhibition. Because of increasing nausea and vomiting, aureomycin administration was discontinued on the 34th day of hospitalization and chloramphenicol therapy resumed. A total dosage of 20.25 gm. was administered during the next seven days. Although four negative blood cultures were reported during this trial of therapy, no improvement was detected clinically, and the temperature continued to range daily between 36 C. (96.8 F.) and 40.2 C. (104.4 F.). Use of chloramphenicol was, therefore, discontinued, and dihydrostreptomycin treatment was resumed. She received a total dosage of 24.5 gm. of this antibiotic for the 10 days preceding her death on the 48th hospital day.

Because of a progressive decline of the total erythrocyte count from 4,100,000 to 3,400,000, with a hemoglobin concentration of 9.5 gm. per 100 cc., the patient was transfused with whole blood on the 38th hospital day. During the period of her hospitalization repeated urine, stool, and sputum cultures were consistently negative for Salmonella organisms. There was little change in the size of the spleen, and no red cells appeared in the urine throughout the course of treatment. Evidence of embolic phenomena was lacking. The 48th hospital day was not unusual until evening, at which time the patient was found to be restless, nauseated, and vomiting. Four hours later she became cyanotic and pulseless, and, when examined, she was found to have died.

The source of infection and the portal of entry were never determined.

4. Bondi, A., Jr.; Spaulding, E. H.; Smith, D. E., and Dietz, C. C.: A Routine Method for the Rapid Determination of Susceptibility to Penicillin and Other Antibiotics, Am. J. M. Sc. **213**:221 (Feb.) 1947.

Autopsy Observations.—The principal findings at autopsy were limited to the heart, mesentery, and small intestine.

The heart weighed 530 gm. The epicardium was smooth, moist, and glistening except for that portion overlying the left atrium, where there was seen a large area of roughening characterized by the presence of varying amounts of grayish-white adhesions and small deposits of fibrin. The apex was moderately rounded. The right side of the heart, including its valvular apparatus, was essentially normal, and the right ventricular myocardium measured 0.4 cm. in thickness. The left atrium was markedly dilated and its wall thickened to measure 0.3 cm. on cross section. Within the atrium were seen several large, firm, friable, whitish to pinkish-red mural thrombi. One of these was large and pedunculated, while others appeared as various-

Heart of patient with Salmonella Endocarditis.

sized, irregularly shaped, sessile excrescences. The thrombi protruded into, and almost completely filled, the cavity. They did not occlude or extend into the pulmonary veins. Around the wide base from which these thrombi arose, the endocardium was bright red to dark red, roughened, and focally ulcerated. The mitral valve was markedly stenotic, presenting an oval orifice which measured not more than 0.7 cm. in its greatest diameter. The free edge and the edge of closure of the mitral leaflets were fibrosed, thickened, and rolled. The commissures were fused by extensive scarring. The chordae tendineae were shortened, thickened, and fused. Arising from the atrial surface of the mitral valve were seen several partially calcified, irregularly shaped, verrucous excrescences which measured not more than 0.4 cm. in diameter. The left ventricle was moderately dilated, and the left ventricular myocardium measured 1.5 cm. in thickness. Approximately 1.5 cm. below the aortic valve on the posterior wall of the left ventricular endocardium was seen along the tract of outflow an irregularly crescent-shaped, thin,

membranous valve-like flap of whitish-gray tissue which measured 1.0 by 0.7 cm. The aortic ring was 5.5 cm. in circumference, and the aortic valve, except for slight irregular atherosclerotic thickening just below the free edge of the cusps, was essentially normal (Fig.).

Microscopic examination of the heart revealed diffuse, mild interstitial myocarditis. This was characterized by the presence of many small, focal, interstitial collections of round cells, consisting chiefly of polymorphonuclear leucocytes, with occasional lymphocytes and monocytes. Also, evidence of cardiac hypertrophy was demonstrated by marked variation in size and shape of myocardial fibers and nuclei. Multiple sections taken through the left atrium verified the presence of fibrinous pericarditis, as well as evidence of myocardial hypertrophy not dissimilar to that described above. The thrombi within the left atrium were composed of fibrin, thrombocytes (platelets), and organizing fibroblasts and capillaries superimposed upon fibrous and hyalinized connective tissue which blended imperceptibly with the underlying myocardium. Several calcareous deposits were contained within these fibrotic areas. Within the endocardium of the atrium was a zone of granulomatous proliferation, consisting of fibroblasts, capillaries, and inflammatory cells.

The serosal surface of the small intestine was smooth, moist, and glistening. Upon dissection, the mucosa of a segment of ileum measuring approximately 1 m. in length was found to be diffusely hyperemic and focally hemorrhagic. The wall did not appear rigid or thickened. The lumen of the bowel contained a small amount of dark-red, thick, mucinous material. Histologic sections through the areas of discoloration revealed extreme hyperemia of the vessels of the wall, with focal hemorrhages into the mucosa. Necrosis was not seen.

Upon dissection of the mesenteric veins, there were found within several of the larger tributaries occasional grayish-red, dull, slightly roughened, firm thrombi which completely occluded the lumens. These, however, were not adherent to the intima of the vessels.

Positive cultures for Salmonella sp. (Type Oranienburg) were obtained post mortem from the liver and spleen.

Anatomic Diagnosis.—The anatomic diagnoses were as follows: healed rheumatic endocarditis of mitral valve, with severe mitral stenosis and insufficiency; superimposed bacterial endocarditis of the mitral valve and left atrium; massive mural thrombosis of the left atrium; splenomegaly; terminal thrombosis of mesenteric veins.

COMMENT

Salmonella sp. (Type Oranienburg), Family Enterobacteriaceae, was first isolated by Kauffmann [2] in 1930, when it was cultured from the stool of an apparently normal inmate during an outbreak of diarrhea in an institution near Oranienburg, Germany. It is a Gram-negative, non-spore-forming, motile bacillus. According to the Kauffmann-White classification,[5] the antigenic formula of this organism is found in Group C_1 and consists of O antigens VI and VII and H antigens, Phase 1, *m* and *t*. Pathogenetically it is grouped with those Salmonella organisms which produce disease in human beings as well as in birds and animals. It has been isolated from chickens [6] and dried egg products [7] and is a natural cause of epizootics in quail.[8] Human infections from which Salmonella sp. (Type Oranienburg) has

5. Breed, R. S.; Murray, E. G. D., and Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology, ed. 6, Baltimore, Williams & Wilkins Company, 1948.

6. Dubos, R. J.: Bacterial and Mycotic Infections of Man, Philadelphia, J. B. Lippincott Company, 1948, p. 383.

7. Solowey, M.; McFarlane, V. H., and Spaulding, E. H.: Microbiology of Spray-Dried Whole Egg: II. Incidence and Types of Salmonella, Am. J. Pub. Health **37**:971 (Aug.) 1947.

8. Edwards, P. R.: The Occurrence of Salmonella, Oranienburg Type, in an Infection of Quail, J. Bact. **32**:259 (Sept.) 1936.

been cultured include gastroenteritis,[9] meningitis,[10] pneumonia and pleurisy,[11] cholecystitis,[9] septicemia without endocarditis,[12] and perirectal abscess.[13]

A thorough review of the available American and foreign literature from 1930 to 1950 fails to disclose any case of bacterial endocarditis from which Salmonella sp. (Type Oranienburg) was isolated. From 1936 to 1950 only 21 cases of Salmonella endocarditis have been recorded, and all have terminated fatally. Four additional unpublished cases have recently been brought to our attention.[14] The organisms isolated from these 25 cases include Salmonella choleraesuis,[15] Salmonella paratyphi B (Salmonella schottmuelleri),[16] Salmonella typhimurium,[17] Salmonella typhi (Salmonella typhosa),[18] Salmonella fayed,[19] Salmonella sp. (Type Thompson),[11] and Salmonella sp. (Type Minnesota).[20] It is of interest to note that S. choleraesuis was cultured in 13 of these 25 cases, emphasizing the high degree of invasiveness of this organism.

The successful use of chloramphenicol in treatment of typhoid, as reported by Woodward and co-authors,[21] indicated that it may favorably influence the course of other Salmonella infections. However, in treating nine children having Salmonella enteritis, Ross and associates[22] found that the pathogens were permanently removed from the stool in only two cases. De Swiet,[17b] employing chloramphenicol

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9. Seligmann, E., and Hertz, J. J.: Salmonella Infections, Report of 37 Cases Observed at Beth Israel Hospital, New York, in the Past 4 Years, Ann. Int. Med. **20**:743 (May) 1944.

10. Hollis, C. H., and Barron, E. W.: Meningitis Due to Salmonella Oranienburg: Report of a Case, J. Pediat. **24**:568 (May) 1944.

11. Saphra, I.: Fatalities in Salmonella Infections, Am. J. M. Sc. **220**:74 (July) 1950.

12. Saphra.[11] Partington, C. N., and Cooper, T. V.: Salmonella Oranienburg Septicaemia: Report of a Further Case, Brit. M. J. **2**:298 (Aug. 7) 1948.

13. Smiley, D. G.; Frank, S. L., and Weil, A. J.: Salmonella Oranienburg in a Perirectal Abscess, J. A. M. A. **143**:430 (June 3) 1950.

14. Saphra, I.: Personal communication to the authors.

15. Saphra.[11] Saphra.[14] Forster, D. E.: Fatal Bacterial Endocarditis Due to Salmonella Suipestifer, Am. J. M. Sc. **197**:234 (Feb.) 1939. Goulder, N. E.; Kingsland, M. F., and Janeway, C. A.: Salmonella Suipestifer Infection in Boston: Report of 11 Cases, with Autopsy Findings in a Case of Bacterial Endocarditis Due to This Organism, and a Study of the Agglutination Reactions in This Infection, New England J. Med. **226**:127 (Jan. 22) 1942. Read, C. T.: Endocarditis Caused by Salmonella Suipestifer, J. Infect. Dis. **65**:263 (Nov.-Dec.) 1939.

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17. (*a*) Saphra.[11] (*b*) De Swiet, J.: Subacute Bacterial Endocarditis Due to Salmonella Typhi-Murium, Brit. M. J. **2**:1155 (Nov. 19) 1949. (*c*) Svab, V.: Endocarditis Lenta Caused by Salmonella Typhimurium Infection, Časop. česk. lék. **79**:1192, 1940.

18. Galbreath, W. R., and Hull, E.: Sulfonamide Therapy of Bacterial Endocarditis: Results in 42 Cases, Ann. Int. Med. **18**:201 (Feb.) 1943.

19. Anderson, E. S.; Anderson, H. J., and Taylor, J.: New Salmonella (Salmonella Fayed) Which Caused Fatal Endocarditis in Man, J. Path. & Bact. **59**:533 (Oct.) 1947.

20. Kurz, E.; Crehan, E., and Thomson, C.: Salmonella Endocarditis with Streptomycin Failure, Ann. Int. Med. **31**:497 (Sept.) 1949.

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22. Ross, S.; Burke, F. G.; Rice, E. C.; Washington, J. A., and Stevens, S.: Chloromycetin in the Treatment of Salmonella Enteritis, New England J. Med. **242**:173 (Feb. 2) 1950.

therapy for a patient with S. typhimurium endocarditis, instituted initial doses of 3 gm. daily. The dosage was progressively increased to 12 gm. a day without influencing the outcome of the disease. In the case we report, chloramphenicol, though effective in vitro against Salmonella sp. (Type Oranienburg), had little effect on the disease process in the dosage used. Despite the fact that negative blood cultures were obtained during chloramphenicol administration, discontinuance of use of the antibiotic was promptly followed on one occasion by reappearance of the organism. King and co-workers [23] reported terramycin to have produced symptomatic improvement in three cases of bacteremia due to S. choleraesuis. The role this antibiotic will play in the future management of Salmonella endocarditis is still to be determined.

SUMMARY

A case of bacterial endocarditis due to Salmonella sp. (Type Oranienburg) is reported. Although effective in vitro, chloramphenicol administration did not alter the clinical course in the dosage used.

23. King, E. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R. B., and Cornely, P. B.: Clinical Observations on the Use of Terramycin Hydrochloride, J. A. M. A. **143**:1 (May 6) 1950.

NONSPECIFIC GRANULOMA OF RECTUM AND SIGMOID COLON

Lesions of Rectum and Sigmoid Colon Which Clinically Simulated Cancer but Which Responded to Aureomycin Therapy

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SIDNEY FOX, M.D.
AND
RALPH ALLEN, M.D.
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A DISCUSSION of the etiological basis for benign granulomatous lesions of the rectum and sigmoid colon usually includes lymphogranuloma venereum, syphilis, tuberculosis, amebiasis, gonorrhea, and schistosomiasis.[1] One encounters infrequently such lesions in a medical ward in a general hospital or in the practice of internal medicine. The differential diagnosis between a benign and a carcinomatous lesion is sometimes difficult. In view of this fact we thought it important to record our experience with two patients who presented this problem.

Two cases of granulomatous lesion of the rectum and sigmoid have been observed. From historical data and the results of physical examination, including proctosigmoidoscopy, the lesions were thought to be malignant, but after thorough study, including biopsy, they were proved to be nonspecific granulomas. The response of these lesions to aureomycin therapy was unexpected and most unusual and saved the patients from a resection of the colon and rectum that would have had to be done because of the mechanical obstruction that the granulomatous process produced.

In the experience of one of us (R. A.) in a busy proctological clinic where lymphogranuloma venereum is commonly seen and the venereal-disease rate is high, this pathological lesion had never been previously encountered. In addition, communications with Mentzer and Gorsch [2] revealed no like experience. Clinically, these granulomas did not simulate any of the specific granulomas that occur in the rectum and sigmoid colon but did look like carcinomatous lesions.

REPORT OF CASES

CASE 1.—C. M., a 26-year-old Negro bus boy, was admitted to the hospital Sept. 20, 1949, with a three months' history of increasingly severe constipation. He was well until May,

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Dr. Allen is attendant in proctology.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Bacon, H. E.: Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment, ed. 3, New York, J. B. Lippincott Co., 1949, Vol. 1, Chap. 9.

2. Personal communication to the authors.

1949, when a cold developed which lasted four weeks. About two and one-half weeks later he complained of aches and pains in the muscles and joints, lasting 10 days. In June, 1949, he noticed the slow onset of constipation, relief of which required frequent use of laxatives, and a decrease in the diameter of his stool, with the presence of red blood on its surface. In addition, there was a gradual onset of cramping abdominal pain and distention, associated with nausea and vomiting. A 15-lb. (6.8-kg.) weight loss was noted. He was then admitted to the Jackson Memorial Hospital, Miami, Fla., Aug. 3, 1949. There, physical examination revealed a large, fixed granulomatous cauliflower mass in the rectum, 2 in. (5 cm.) above the pectineal line. A polypoid mass was seen above this area, with numerous ulcerations on the rectal and bowel mucosa. Laboratory studies at Jackson Memorial Hospital showed a 3+ Kahn reaction, a negative Frei reaction, and normal blood count and urine. Repeated stool studies failed to yield Endamoeba histolytica. Three biopsy specimens were taken and reported as granulomatous tissue. A roentgenogram with a barium sulfate enema revealed multiple polypoid filling defects and suspicious small areas of mucous ulcerations in the descending colon and sigmoid. Therapy included 100,000 units of penicillin every three hours for 13 days, ½ grain (0.03 gm.) of emetine hydrochloride daily for 10 days, and 2 gm. of diiodohydroxyquinoline (diodoquin®) daily for 25 days, but no clinical improvement occurred. He was then transferred to this hospital on Sept. 20, 1949.

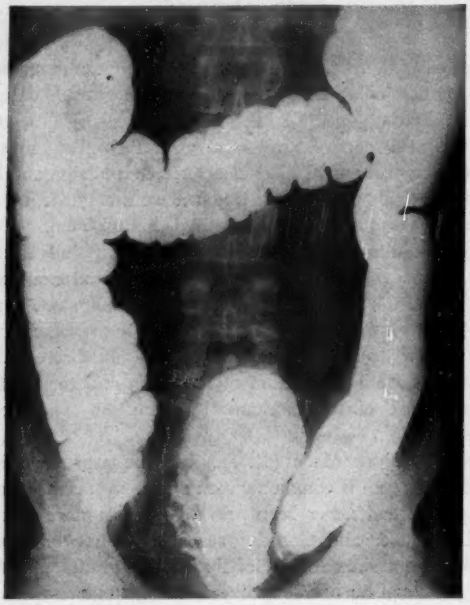

Fig. 1 (Case 1).—Irregular filling of distal portion of rectum and sigmoid colon with barium sulfate suspension.

Physical examination at this time revealed a well-developed and normal Negro man in no apparent distress. His height was 5 ft. 6 in. (167.6 cm.), and his weight, 163 lb. (74 kg.). Pea-sized inguinal nodes were present. On rectal examination a hard mass was palpable on the right side of the rectum which was barely reached by the finger tip. No penile scar was noted. The results of the remainder of the physical examination were normal.

Laboratory examinations revealed a negative blood Kahn reaction and a white-blood-cell count of 7,180, with 64 polymorphonuclear forms, 27 lymphocytes, 6 monocytes, and 3 eosino-

phils. The total protein was 7.1 gm. per 100 cc., with 3.37 gm. of albumin and 3.73 gm. of globulin. Complement-fixation tests for lymphogranuloma venereum on two occasions and for amebiasis gave negative results. Four stool examinations failed to reveal any ova or parasites. Roentgenography with a barium sulfate enema on Sept. 23 (Fig. 1) revealed irregular filling of the distal part of the rectum and distal portion of the sigmoid colon, with distortion of the mucosal pattern and narrowing of the lumen for an area extending 12 cm.

A biopsy specimen taken on Oct. 20 was reported by the pathologist, Dr. Alfred Blumberg, to show the following:

"Several pieces of tissue presented the same picture with minor variations. The epithelial lining as well as the glandular epithelium was of natural appearance. These were supported by a matrix in which the inflammatory reaction consisted of the presence of small cells and of an increased number of capillary blood vessels. In one area there was an indication of the presence of a small ulcer, the gap of which was filled with polymorphonuclear leucocytes,

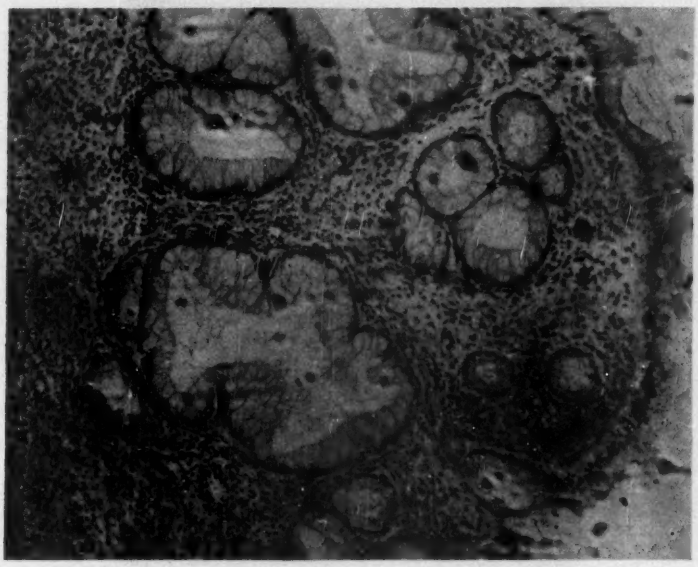

Fig. 2 (Case 1).—Section of tissue revealing inflammatory reaction; diagnosis was nonspecific granuloma.

among which a number of eosinophils was seen. There was no evidence of malignant growth anywhere. The diagnosis was granuloma, nonspecific" (Fig. 2).

The patient was afebrile during his hospital course. Diagnostic investigation was carried out to determine the causation of the granulomatous mass. Several possibilities were considered, such as lymphogranuloma venereum, schistosomiasis, amebic granuloma, neoplasm, and tuberculosis.

Sigmoidoscopic examination on Sept. 21 revealed a fungating, firm, friable mass at 6 cm. on the anterior and right lateral wall of the rectum. Treatment was started with aureomycin, 500 mg. every six hours orally and 300 mg. intravenously daily. One week later a second sigmoidoscopy revealed the lesion to be about the same size; however, it was not quite so angry in appearance. Aureomycin therapy was continued. Sigmoidoscopy on Oct. 12 revealed that the mass was smaller and less fungating. During this examination it was possible for the first time to insert the sigmoidoscope beyond the original lesion. Three small lesions were seen;

two were the size of a pea, and the third was about the size of a grape. All these lesions appeared as polyps, with reddened reaction at the base. The rectal mucosa between the areas appeared normal.

By Oct. 6, two weeks after therapy with aureomycin, the patient felt much better. He lost his abdominal cramps, and his appetite increased. He gained weight and had two normal bowel movements daily. On Nov. 2 sigmoidoscopy revealed a marked improvement in all the lesions. He was discharged Nov. 3 and was advised to continue taking aureomycin, 1 gm. daily for two weeks, and then 0.5 gm. daily for an additional two weeks. The total dosage of aureomycin was 111.3 gm.

Recheck sigmoidoscopy was accomplished Dec. 7, 1949. The sigmoidoscope was inserted to 8 cm.; the site of the original large fungating, friable mass. The only evidence of this mass

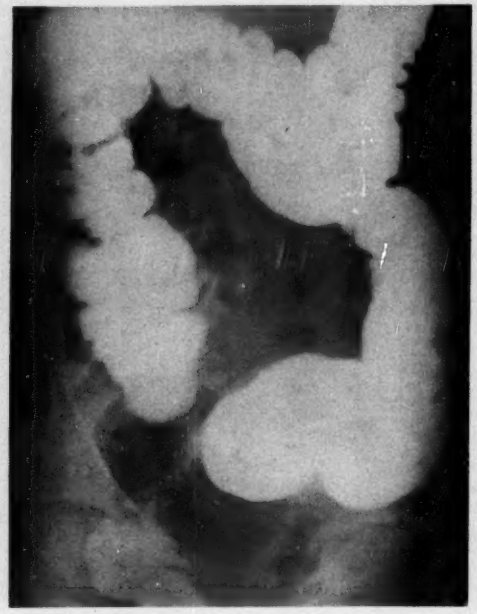

Fig. 3 (Case 2).—Roentgenogram during barium sulfate enema, revealing segment of narrowing in rectum.

was one mucosal fold that was fibrotic and firm, but not fixed. There was no evidence of ulceration, and the other small lesions above the original large mass were no longer present.

Case 2.—G. B., a 24-year-old Negro farm worker, was admitted to the hospital April 19, 1950. He was well until three months prior to admission, when he began having a dull, aching sacral pain. Gradually, anorexia, weight loss, and severe constipation followed. Occasionally nausea was noted, but no vomiting was present. Cathartics were used to promote daily bowel function. Fever was present one month prior to admission and persisted. The sacral pain became increasingly severe and began radiating over the back of the left hip. Weakness was progressive and became severe. There was a weight loss of 37 lb. (16.8 kg.). No history of the stigmata of syphilis was obtained.

On admission the temperature was 101 F., the pulse rate 112, the respiratory rate 18, and the blood pressure 130/80. The patient was emaciated but not cachectic. The liver and spleen were not palpable, and there was no adenopathy. The muscles of the lower part of the back

were spastic. Normal male genitalia were present, and no penile scar was found. Superficial and deep reflexes were physiological, and no neurological changes were noted. The rectal examination revealed firm, but not hard, granulations on the anterior wall of the rectum above the prostate. Higher up, the rectal wall was encircled by a firm, roughened mass, almost obliterating the lumen; blood was noted on the examining finger.

Sigmoidoscopy revealed the perianal skin and the sphincter tone to be normal. The rectal wall was edematous and indurated, with a firm cartilaginous feel. The lesion began 1 in. (2.5 cm.) above the pectineal line, extended upward, and almost completely occluded the lumen of the rectum.

The white-blood-cell count was 20,950, with 69 polymorphonuclear forms and 25 lymphocytes. The hemoglobin concentration was 6.0 gm. (Haden-Hausser method); the red-blood-cell count was 2,450,000, and the sedimentation rate was 20 mm. per hour, corrected (Wintrobe). The total protein was 8.70 gm. per 100 cc., with 3.55 gm. of albumin and 5.15 gm. of globulin.

Fig. 4 (Case 2).—Section of tissue revealing discrete granulomas in subepithelial layers.

Blood agglutinins for Salmonella typhosa, Salmonella paratyphi A and B (Salmonella schottmuelleri), and Brucella abortus were normal, and the Weil-Felix reaction was negative. Three stools were negative for ova and parasites. The blood serum was negative for complement-fixing antibodies of the psittacosis-lymphogranuloma venereum group, and the Frei reaction was negative. A blood Kahn test showed 16 Kahn units, and the Kolmer reaction was also positive. The spinal fluid was positive for syphilis in the first dilution only, with a gold curve of 0120000000.

The roentgenogram with a barium sulfate enema was not done until July 1, 1950. It showed a segment of narrowing and persistent spasm in the upper part of the rectum, measuring approximately 2 cm. in length, with a normal mucosal pattern. The findings were interpreted as being consistent with the presence of an inflammatory process of the upper rectum (Fig. 3).

A biopsy specimen (Fig. 4) was reported by the pathologist, Dr. Harold W. Keschner, to show the following:

"Section revealed areas of intact mucosa alternating with adjacent zones in which there was replacement of mucosa by granulation tissue and fibrin debris. While the mucosa was intact,

the lamina propria was well infiltrated with lymphocytes and large mononuclear cells. Throughout the subepithelial tissue there were discrete granulomas which were characteristically composed of lymphocytes, large mononuclear cells, and histiocytes, apparently reticuloendothelial in origin. Plasma cells were not numerous. There was extensive collagenization of the interstitial stroma. The diagnosis was granuloma, cause undetermined. Special stains for bacteria, fungi, and protozoan organisms were negative."

Aureomycin [3] therapy was begun on the second hospital day, the dosage being 500 mg. given intravenously every 12 hours for five days and then 500 mg. given orally every six hours for 35 days. This was reduced to 250 mg. four times daily for another 42 days. The total dosage was 117 gm.

On the fourth hospital day the patient's temperature returned to normal and remained normal throughout the remainder of hospitalization. Subsacral pain decreased, and the appetite returned. On the sixth hospital day he felt stronger, had no pain, and had two normal-sized bowel movements. Rectal examination showed some improvement, in that the granulations had decreased in size and the constriction higher up seemed to be less. Also, no blood was returned on the examining finger. By the 22nd hospital day, the lesions showed marked improvement. Antisyphilitic therapy (penicillin) was begun on the 29th hospital day and continued for a total dosage of 9,000,000 units. By the 41st hospital day the patient had gained 30 lb. (13.6 kg.) in weight. The last sigmoidoscopy, on the 80th hospital day, revealed the persistence in the rectum of small granulations with a rubbery feel; however, the mucosa was now pink instead of white and edematous. On the 83rd hospital day, July 10, 1950, he was given leave from the hospital, but he failed to return, and subsequent attempts to locate him were unsuccessful.

COMMENT

Review of the literature for the past 15 years reveals only one other report [4] of a case that appeared to be similar to the ones described. In that study the granuloma did not respond to sulfonamide of penicillin therapy, and a resection of the sigmoid colon and rectum was done, with apparent complete recovery. No definite cause for the lesion was found, and the author emphasized the pseudocancerous appearance of the tumorous mass.

In the present two patients we attempted to rule out any specific cause for the tumors. Clinically, the lesions did not look like lymphogranuloma venereum and several biopsy specimens studied by different pathologists (Dr. P. Rezik,[2] Dr. A. Blumberg,[2] Dr. W. Sheldon [2]) proved that lymphogranuloma was not present. Interestingly enough, both patients had fever and increased serum globulin, but the Frei test and complement-fixation examination of the serum gave negative results.

Amebiasis [5] may cause a granulomatous process in the rectum; studies of the stools and pathological slides revealed no amebas. Furthermore, the first patient had a course of intensive antiamebic therapy without any clinical improvement. Because of this experience, a clinical trial of antiamebic therapy was not attempted for the second patient.

Both patients had positive Kahn reactions in relatively low titer, but neither had any historical or clinical stigmata of syphilis. Grossly, the granulomas did not look syphylitic; in addition, syphilitic lesions of the rectum and sigmoid are rare even in a highly syphilitic population. The slides of pathological material did not

3. Aureomycin was furnished through the courtesy of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

4. Mangoni, A. R.: Specific Inflammatory Rectosigmoiditis of Pseudo-Cancerous Form, Bol. Soc. cir. Rosario **15**:111-116, 1948.

5. Hawe, P.: Amebic Infection of the Rectum Simulating Carcinoma, Liverpool Med.-Chir. J. **50** (Pt. 1):35-44, 1946.

suggest the lesions of syphilis. In spite of this, the first patient was given an adequate course of penicillin therapy, with no improvement.

Tuberculosis was ruled out by the biopsy specimens, the negative tuberculin skin test reactions, and the clinical survey, including roentgenograms of the chest.

The presence of schistosomiasis, gonorrhea, and other bacterial etiological agents of the granulomas was ruled out by appropriate stool studies, gross appearance, and biopsy.

The history of gradually increasing obstipation, with blood in the stools, along with the gross appearance and feel of these tumors, suggested neoplastic lesions. The marked asthenia, loss of weight, and fever made the diagnosis of carcinoma most likely. In fact, it was the working hypothesis in the study of both patients; only after repeated biopsy was our attention turned to other possibilities.

In the first patient aureomycin treatment was tried only after thorough antiamebic and antisyphilitic therapy. The response was fairly rapid, and when he was last seen he was in perfect health. Because of this experience, the second patient was given aureomycin as soon as the pathological sections were secured. His condition improved rapidly thereafter, but he left the hospital before a complete clinical cure was obtained. We feel that both patients have remained well; otherwise they would have returned, as the Veterans Administration Hospital offers them the best facility for therapy.

One can only speculate on the etiological basis of the lesions described. That the tumors responded to aureomycin treatment and not to other antibiotic therapy may make one consider a virus as the causative agent. No viral cultures or studies for complement-fixing or neutralizing antibodies were done.

We feel that it is important to emphasize the clinical similarity of these granulomas to carcinoma of the rectum and sigmoid colon. It is necessary to try aureomycin treatment for all granulomas in this region of the intestinal tract when the pathological studies reveal no evidence of specific disease or of malignant growth, or are questionable; as in our experience, one may save the patient from a resection of the rectum and sigmoid colon.

SUMMARY

Two cases of nonspecific granulomas of the rectum and sigmoid colon are presented. The clinical similarity of these lesions to carcinoma is emphasized. Cure of these lesions with aureomycin therapy is described. It is important that aureomycin therapy be given in all cases of nonspecific granuloma of the rectum and sigmoid colon before resection is considered.

ADDENDUM

CASE 2.—G. B. returned to the Veterans Administration Hospital in May, 1951. This time he had an atypical pneumonia which responded to aureomycin therapy. Proctoscopic examination and a roentgenogram with a barium sulfate enema revealed the colon to be normal. All evidence of the lesions previously described had disappeared, and the mucous membrane of the rectum and sigmoid directly visualized was perfectly normal.

FAT EMBOLISM

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WICHITA, KAN.

THE CLINICAL recognition of the presence of fat embolism as a complication of tissue trauma is becoming increasingly more important. Zenker, whose work was cited by Warthin,[1] first described the condition in 1862, and 86 cases were reported in the literature of the following 17 yr. It was Warthin's opinion [1] that fat embolism resulting from traumatic lipemia was not rare, the condition being the most frequent cause of death following fracture of long bones when infection was not present. Magendie, whose work was also cited by Warthin,[1] during the period 1821 to 1836 performed many experiments on animals, in which olive oil was introduced intravenously, and discovered that fluid fat, such as olive oil, could not pass through the smaller vessels but blocked them mechanically. He apparently was not aware that fat emboli occurred in man.

It is the purpose of this paper to redirect attention to this entity by a review of its clinical manifestations and pathogenesis and to present an illustrative case showing typical clinical and postmortem findings.

A review of the literature reveals that two main groups of conditions are associated with fat embolism, as classified by Vance.[2] The first group, in which the etiological connection is unquestioned, includes trauma to the adipose tissues of the body and the intravenous injection of oily substances. With trauma to the adipose tissues is included injury to the osseous system, such as fractures of long bones and orthopedic operations, trauma to the subcutaneous and intermuscular fat, and trauma to fatty viscera. Several cases have been described as following surgical procedures, such as cholecystectomy or abdominoperineal resection, on adipose patients.[3] The second group, in which the etiological connection is doubtful, includes burns, poisonings, postmortem processes, and natural causes of death producing fatty necrosis. Other etiological factors that have been mentioned in the literature [3b] include osteomyelitis, diabetes mellitus, eclampsia, pancreatitis, and tuberculosis.

Dr. Carreau is Resident in Surgery, and Dr. Higgins is Chief of the Surgical Service, Veterans Administration Center.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not reflect the opinion or policy of the Veterans Administration.

1. Warthin, A. S.: Traumatic Lipemia and Fatty Embolism, Internat. Clin. **4**:171-227, 1913.

2. Vance, B. M.: The Significance of Fat Embolism, Arch. Surg. **23**:426-465 (Sept.) 1931.

3. (*a*) Robinson, J. R.: Fat Embolism Following Abdominal Surgery, Am. J. Surg. **78**:401-405, 1949. (*b*) Denman, F. R., and Gragg, L.: Fat Embolism: Diagnostic Enigma, Arch. Surg. **57**:325-332 (Sept.) 1948. (*c*) Gurd, F. B.: Conditions Affecting Risk of Operation—General Considerations, S. Clin. North America **25**:1015-1026, 1945. (*d*) McGrath, E. J.: Postoperative Pulmonary Complications, ibid. **25**:1190-1201, 1945.

PATHOGENESIS AND SYMPTOMATOLOGY [4]

The clinical manifestations of fat embolism are primarily pulmonary or cerebral, or both, although dissemination of the fat globules is rather widespread throughout the body. Reasons for the clinical picture will become apparent as the pathologic changes are described.

The pathogenesis of this condition is felt to be a disintegration of the supporting fibrous tissues of the bone-marrow fat or adipose tissue, with liberation of fat globules.[5] Ruptured blood vessels must be present in the vicinity. Arteries bleed into this space, increasing the pressure, and the veins that remain open absorb the fatty mixture by venous suction. Gauss [6] pointed out that fat embolism is common with fractures because the veins are surrounded by a bony wall and cannot collapse as they can elsewhere in the body.

By the very nature of the pathogenesis of this condition, considerable free fat may enter the venous circulation, where it is transported to the heart and then to the lungs. The fat emboli block many of the capillaries of the pulmonary tissues, resulting in edema, hyperemia, minute hemorrhages, and eventually leucocytic infiltration. Generalized hemorrhage into the alveolar spaces, as exhibited in the case described below, may account for the progressive, profound anemia frequently observed. These pathologic changes produce a clinical picture that may appear in three to four hours or may be delayed as long as three to eight days. The symptoms may vary from slight irritability and excitability to maniacal periods. The pulse rate and temperature may rise; the former may become feebler, and the temperature may increase to 106 to 107 F. The respiratory rate increases more rapidly than the pulse rate, with an associated pallor, dyspnea, and cyanosis. Moist rales may appear with a cough producing material that may or may not be blood-stained. The condition at this time may be confused with bronchopneumonia.

If the quantity of fat reaching the lungs is small, the globules will be filtered out of the circulation, and clinical manifestations will be mild or absent. If the quantity is large, estimated by Lehman and Moore [7] to be approximately 120 cc. in man, the fat emboli pass through the capillaries of the lung, return to the heart, and then enter the systemic circulation to be widely disseminated throughout the body. If the emboli enter the coronary circulation, the smaller vessels become occluded, resulting in engorgement and hyperemia of the cardiac musculature. This is manifested clinically by rapid, feeble pulse and a drop in the blood pressure. There may be widespread discrete deposition of fat globules throughout the central nervous system, usually producing cerebral signs without localization. The manifestations include

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4. (*a*) Warthin.[1] (*b*) Vance.[2] (*c*) Scuderi, C. S.: Fat Embolism: Clinical Experimental Study, Surg., Gynec. & Obst. **72**:732-746, 1941. (*d*) Warren, S.: Fat Embolism, Am. J. Path. **22**:69-87, 1946. (*e*) Newman, P. H.: Clinical Diagnosis of Fat Embolism, J. Bone & Joint Surg. **30B**:290-297, 1948. (*f*) Gauss, H.: The Pathology of Fat Embolism, Arch. Surg. **9**:592-605 (Nov.) 1924. (*g*) Groskloss, H. H.: Fat Embolism, Yale J. Biol. & Med. **8**:49-91, 1935. (*h*) Scuderi, C. S.: Present Status of Fat Embolism, Internat. S. Digest **18**:195-215, 1934.

5. Miloslavich, E. L.: Fat Embolism, Medico Legal Aspects, Wisconsin M. J. **29**:139-143, 1930.

6. Gauss, H.: Studies in Cerebral Fat Embolism, Arch. Int. Med. **18**:76-102 (July) 1916.

7. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production Without Trauma, Arch. Surg. **14**:621-662 (March) 1927.

restlessness, headache, drowsiness, vomiting, stupor, hallucinations, coma, spasm, convulsions, paralysis, and high fever. Terminally, Cheyne-Stokes respirations may be present. Differentiation from traumatic intracranial injuries may be difficult, since many of these patients have been in accidents producing generalized injury. Fat emboli to the skin may produce petechial hemorrhages most prominent over the abdomen, thorax, neck, and conjunctiva. If there is kidney involvement by the fat emboli, lipuria may be present.

DIAGNOSIS [8]

The clinical manifestations may be so minimal, as in the majority of cases, that symptoms are absent, or they may be so severe that death results in a few hours to a few days. The clinical diagnosis of fat emboli is justified only if there is a history of an injury causing a fracture of a long bone or severe soft-tissue trauma. A period without symptoms or signs may precede the interval of pulmonary and central nervous system changes. Occasionally, there may be an alternating elevation and

Clinical and Laboratory Manifestations of Fat Embolism

	Symptoms and Signs	Laboratory Findings
Pulmonary Phase	Fracture of long bone or evidence of fatty-tissue trauma	Progressive anemia
	Interval following accident with no signs or symptoms	Significant roentgen findings in chest
	Cyanosis, dyspnea, stertorous breathing, moist rales, blood-tinged expectoration	
	Temperature of 102 F. or more	
	Blood pressure raised or normal	
	Increased pulse rate with more rapid increase of respiratory rate	
	Cardiac failure due to deposition of fat globules in coronary circulation	
Cerebral (Systemic) Phase	Headache, vomiting, hallucinations, coma, spasm, tremor, delirium, restlessness, stupor, convulsions, maniacal episodes	Dark-field examination of blood for fat globules
	Alternate elevation and depression of conscious state	Fat globules in urine
	Petechial hemorrhages over chest, abdomen, conjunctiva, and fundus	
	Fat globules in retinal vessels	
	Possible presence of Babinski sign	
	Possible presence of focal paralysis	
	Rapid, weak, irregular pulse	

depression of the conscious state. The temperature is usually 101 to 102 F. and may increase to 106 F. The blood pressure may be normal or elevated. Petechial hemorrhages may be present about the neck, chest, abdomen, and conjunctiva. Occasionally, fat globules may be observed in the retinal vessels. The laboratory may be of aid in arriving at the diagnosis. Microscopic examination of the last few cubic centimeters of a urine specimen may reveal the presence of fat droplets. Examination of saliva for fat droplets, as suggested by Warthin,[1] is not reliable, because fat may be present in normal saliva.[4c] Scuderi has reported that a dark field examination of the blood may be of great diagnostic aid in disclosing the presence of fat droplets in the blood stream. In 1936, Jirka and Scuderi showed for the first time the value of chest roentgenograms in the detection of injected oleic acid and olive oil in dogs. These men were of the opinion that if fat droplets are present in sufficient quantity in the blood stream there will always be changes in the lung fields detectable by roentgenogram. A clinical diagnosis of fat embolism is

8. Footnote 4*c*, *e*, and *f*.

difficult to make. It can be accomplished only if the possibility of the condition is kept in mind on review of the symptoms and signs the patient presents. In differential diagnosis [9] one should include brain concussion, skull fracture, cerebral compression, secondary shock, delirium tremens, crush syndrome, bronchopneumonia, blast injury, anesthetic complications, heat exhaustion, diabetic coma, septicemia, and acute and chronic alcoholism. The chest film and the microscopic examination of the urine are the most reliable diagnostic aids.

TREATMENT AND PROGNOSIS [10]

Preventive measures are probably of most value in the treatment of this condition. Fractures of long bones should be immobilized early. In suspected cases,

Fig. 1.—Roentgenogram of right leg.

supportive therapy should include oxygen and antibiotics and whole blood or plasma should be given for shock, if present. Once the diagnosis has been established, no definite, effective specific therapy is available.

Intravenous saponification of the fat globules, proximal venous ligation, and the application of tourniquets above fractures have proved to be of little therapeutic value. Some authorities feel that most patients with fat emboli recover because the

9. Warthin.[1] Scuderi.[4c] Newman.[4e]

10. (*a*) Scuderi.[4c] (*b*) Newman.[4e] (*c*) Kingsbery, L. B., and Wilkinson, A. B.: Massive Fat Embolism with Recovery, Ann. West. Med. & Surg. **1**:186-190, 1947. (*d*) Spriggs, J. B., and Moore, E.: Fracture of the Right Tibia with Fat Embolism to Brain, Lungs, Kidney, Skin and Conjunctiva, Am. J. Clin. Path. **19**:388-392, 1949.

mild cases are overlooked and only the extremely severe and fatal cases are diagnosed. However, there have been several severe cases reported with recovery.[11]

REPORT OF CASE

A. C. D., a 23-yr.-old white man, was admitted to this hospital on Dec. 17, 1950, by transfer from a local community hospital, with the history of having been involved in an automobile accident 36 hr. earlier. The case summary from the outside hospital covering the previous 36 hr. is as follows:

On admission to the emergency room, the patient appeared to be in a somewhat dazed condition and was also under the influence of alcohol. Physical examination revealed multiple contusions and abrasions, with a large hematoma over the right eye and temple. There were also a severe laceration of the anterior portion of the right knee and an obvious fracture of the right

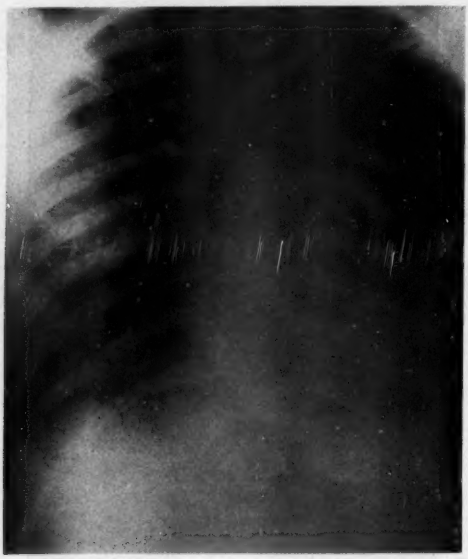

Fig. 2.—Chest roentgenogram made with portable x-ray, showing multiple floccular densities.

tibia and fibula at the junction of the middle and lower thirds. There was no evidence of shock. The patient was then taken to surgery, where, while he was under light thiopental (pentothal®) sodium anesthesia, the fractures were reduced and a cast was applied. Penicillin therapy was started. On the following morning the patient was well oriented and was reading magazines. Progress was satisfactory until the evening of the first day, when the patient became somewhat apprehensive and his temperature increased to 102.4 F. By midnight the patient was drowsy and stuporous and would arouse only when spoken to. This stuporous condition increased hourly, and it was the impression of the attending physician that the patient might have a cerebral hemorrhage. A spinal puncture revealed essentially normal findings.

On arrival at this hospital 36 hr. following the accident, the patient was in a comatose condition, being roused only on painful stimuli. The right leg was in a midthigh cast. The temperature was 102.2 F. rectally; the pulse rate was 120, and the respirations numbered 30

11. Kingsbery and Wilkinson.[10c] Bourne, G. C., and Schwab, R. S.: Cerebral Fat Embolism: Report of Case with Recovery, Arch. Neurol. & Psychiat. **62**:355-357 (Sept.) 1949.

per minute and were labored. The patient was expectorating blood-tinged sputum. Moist rales were present at the bases of both lungs. The blood pressure was 110/70. The Babinski sign was present on the left, the sign on the right being unobtainable because of the cast. A few petechial hemorrhages were observed over the upper abdomen and chest. Urinalysis showed no abnormalities. A red-blood-cell count was 4,550,000, with 13.8 gm. of hemoglobin. The white-blood-cell count was 12,600, with 88% neutrophils and 12% lymphocytes. The patient was given fluids parenterally, antibiotics, and oxygen therapy. A chest roentgenogram made with a portable x-ray was reported as showing a peribronchial floccular type of infiltration, probably due to emboli.

On the following day the patient's level of consciousness seemed about the same, although the respirations were more rapid and labored. The pulse rate continued to be rapid and the temperature elevated. There were numerous petechial hemorrhages over the chest and abdomen. Results of a second set of laboratory examinations were reported as follows: The urine gave an acid reaction; the specific gravity was 1.027, with a 1+ reaction for albumin. Microscopic

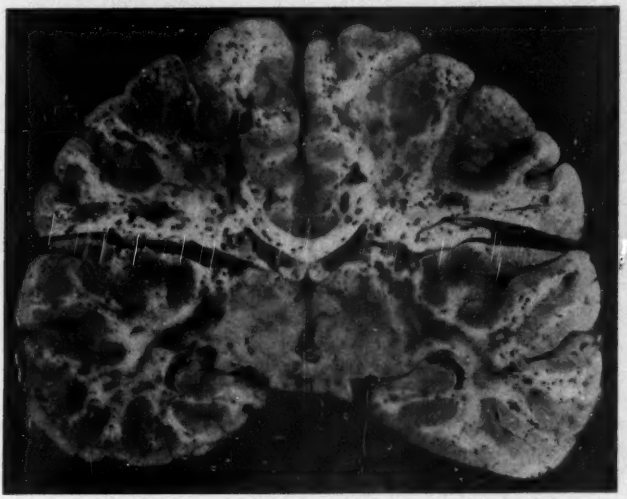

Fig. 3.—Cross section of brain, showing multiple punctate hemorrhages.

study showed a rare red blood cell and numerous crystals of undetermined nature. The red-blood-cell count was 3,170,000, with 9 gm. of hemoglobin. The white-blood-cell count was 8,800, with 80% neutrophils and 10% lymphocytes. The blood urea nitrogen, total protein, bilirubin, carbon dioxide-combining power, and total base were normal. A blood culture was negative for pathogens. Another chest film made with the portable x-ray showed an increase in the previously described peribronchial floccular infiltration. The patient's subsequent course in the hospital was gradually but steadily downhill. The rectal temperature varied between 102.2 F. on admission and 105 F. terminally. The pulse rate ranged from 120 to 155 terminally. The respiratory rate ranged from 35, with a gradual increase, to 60 per minute terminally. Copious quantities of bloody mucus were aspirated frequently from the nose and trachea. The systolic blood pressure gradually increased to 166 mm. Hg terminally. On Dec. 20 the red-blood-cell count was 2,500,000, with 7 gm. of hemoglobin, even though the patient had received 2,000 cc. of whole blood during the previous 48 hr. The white-blood-cell count was 14,650, with 93% neutrophils and 7% lymphocytes. A second spinal tap was performed, with normal findings. A tracheotomy was accomplished on Dec. 20 to facilitate adequate aspiration of the trachea. Moderate quantities of bloody mucus and clotted blood were aspirated at this time. On the morning

of Dec. 20 administration of cortisone (cortone®) acetate in 100-mg. doses was started. A total of 300 mg. was given, with no apparent change. Despite vigorous oxygen therapy, the patient continued to be cyanotic. The general course continued downhill, and the patient died at 11 p. m., Dec. 20, 1950, five days following the original injury.

Autopsy Observations.—The external examination revealed a well-developed, well-nourished white man, with multiple small contusions and abrasions and a reduced fracture of the right tibia and fibula. Multiple petechiae, 2 mm. in diameter, were present over the abdomen, chest, and lower-neck region. The right lung weighed 1,900 gm. and the left 1,700 gm. They were similar in appearance, being firm and rubbery in consistency, with slight crepitation in the anterior portion of each apex. The cut surfaces of the lower lobes revealed a diffuse dark-red coloration

Fig. 4.—Photomicrograph of brain, showing fat emboli. Scarlet red (Sudan IV) stain; × 150.

without structural markings, resembling the appearance of spleen. A dark-red oily fluid exuded from the surface. The trachea and bronchial tree contained frothy blood-tinged fluid. On opening the cranial vault, there was no evidence of a skull fracture or of free blood in the subdural spaces. The brain weighed 1,790 gm., and the surface appeared somewhat congested. On cut section multiple petechiae, 1 to 2 mm. in diameter, were present throughout the white matter of the cerebrum. Microscopic sections of the lung, kidney, and brain, stained with scarlet red (Sudan IV), showed distinct sudanophilic droplets in the vessels of those organs. Routine hematoxylin-eosin staining revealed interalveolar hemorrhage in all sections of the lung, which in some areas was quite marked. The alveolar walls were somewhat thickened, and the alveoli were filled with pigmented and nonpigmented macrophages and hyperplastic alveolar cells. In some sections the alveolar ducts were lined by a thick layer of dense eosinophilic material not unlike hyalin. On examination of the kidney sections, fine and coarse clear vacuolations were

noted in the glomeruli. The multiple punctate hemorrhages in the brain had an oval outline, with a vessel or degenerating matter in the center. Several hemorrhagic areas were surrounded by small areas of degenerating white matter. In still other sections, large areas of diffuse hemorrhage were seen. Ring hemorrhages were seen in the cerebellar cortex and medulla.

COMMENT

It is noteworthy that this patient's condition was refractory to all forms of therapy, the hospital course being steadily and progressively downward. The outstanding features of the case were (1) coma, (2) the progressive rise in respiratory and pulse rates, with progressive cyanosis despite oxygen therapy, and (3) the rapidly progressive anemia in spite of 2,000 cc. of whole blood replacement, the only apparent area of blood loss being through the tracheal-bronchial tree.

There would seem to be little reason to expect beneficial results from cortisone acetate therapy in fat embolism. The use of cortisone acetate in this case was begun rather late, when the patient's condition seemed refractory to all other forms of treatment. The experience with the drug in this case would not justify any conclusion concerning its therapeutic value in fat embolism.

SUMMARY

A review of the laboratory and clinical aspects of fat embolism is presented, along with a case report illustrating the typical findings in this condition.

Autopsy observations are presented through the courtesy of Dr. Richard Crary.

News and Comment

GENERAL NEWS

Teaching Mission Sent to Israel and Iran.—A medical teaching mission which is a joint project of the World Health Organization and the Unitarian Service Committee has been sent from Geneva, Switzerland, to Israel and Iran at the request of the Ministries of Health of the two countries. It includes a public health unit, which will remain in Israel for two months, and clinical and preclinical specialists, who will go to Iran for three weeks after spending a month in Israel. The mission is composed of 14 specialists under the chairmanship of Dr. Leo M. Davidoff, professor of neurosurgery, New York University. Members will work directly with specialists in their respective fields in both Israel and Iran, exchanging information, giving lectures and conferences, and visiting hospitals, clinics, schools, and other medical installations throughout the country.

ANNOUNCEMENTS

Fellowships Offered by The National Foundation for Infantile Paralysis.—The National Foundation for Infantile Paralysis announces the availability of a limited number of additional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biological and physical sciences. The purpose of these National Foundation fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems of poliomyelitis and other crippling diseases.

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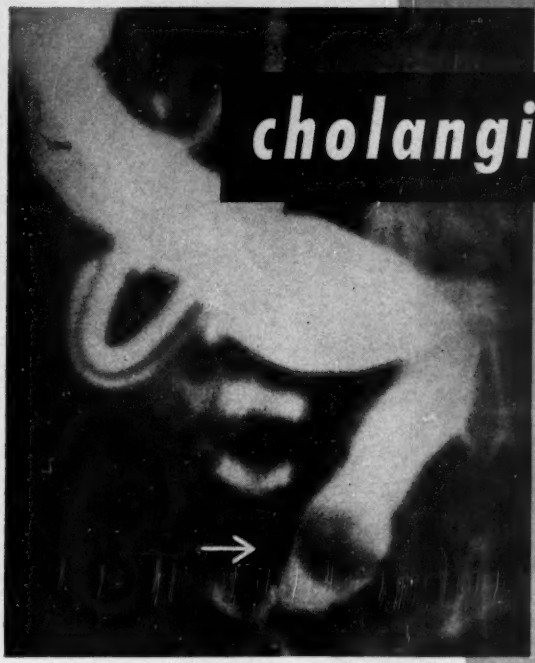
Complete information concerning qualifications and applications may be obtained from Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5.

cholangiography



Cholangiogram with Diodrast 35% showing stone in distal end of common duct. Illustration, courtesy of Dr. J. Buckstein, author of "The Digestive Tract in Roentgenology" (Lippincott, 1948) in which a whole chapter is devoted to this procedure.

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1. Byrne, R. V.: *Amer. Jour. Surg.*, 78:514, Oct., 1949.
2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: *Amer. Jour. Surg.*, 78:347, Sept., 1949.

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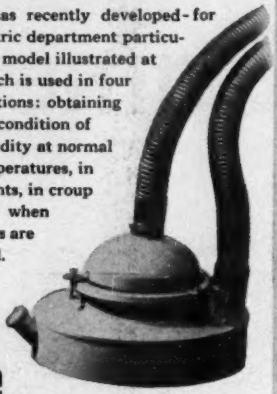

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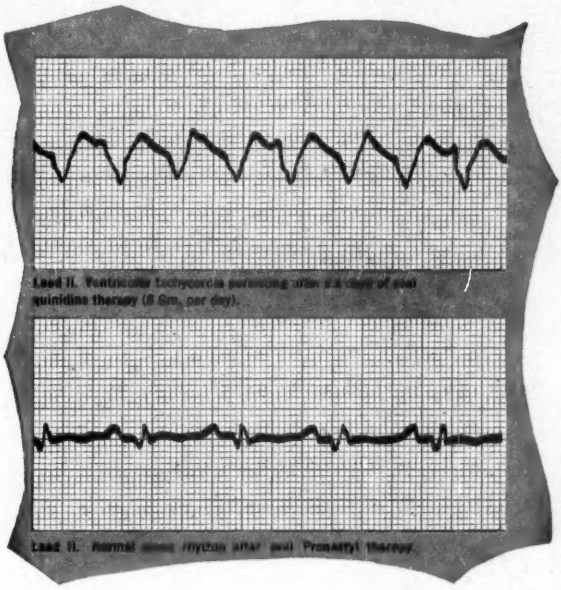

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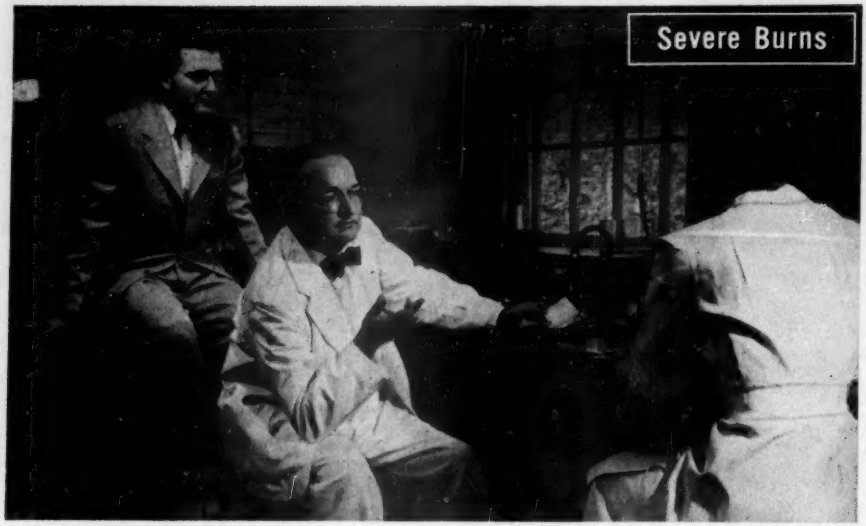

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In a case reported early this year, the fluid loss for the first 24 hours was estimated at 10,000 cc.; the patient received 9,000 cc. of plasma, as well as dextrose and electrolytes; made a remarkable recovery from a burn that covered over 70 per cent of his body surface. Perhaps you read about the case. It was reported by Whitelaw in the Journal of the American Medical Association, January 13, 1951*... one of the first reports (if not the first) on the influence of ACTH in the treatment of severe burns. Further information about this case, four others by the same author, and several cases of severe burns reported by other investigators are contained in a new publication of interest to every physician: "Proceedings of the Second Clinical ACTH Conference," Philadelphia, Blakiston Co., 1951.

How Much Plasma?

We do not know how Whitelaw estimated the fluid loss in that case. The method we suggest is this:

Give 100 cc. of plasma for each per cent of body surface burned (to all patients with 10 per cent or more of the skin area burned).

Half the dose is given in the first 4-6 hours, one quarter in the next 6 hours, and the remainder in the next 12 hours.

It should be borne in mind that the method suggested is merely a rough guide for estimating the probable needs of patients.

LYOVAC® Normal Human Plasma (Irradiated) is administered at the rate of 40 to 60 drops per minute. In emergency, this rate may be increased without reaction.

Lyovac Normal Human Plasma Irradiated

Portable and stable without refrigeration, LYOVAC Normal Human Plasma (Irradiated) is prepared according to the requirements of the National Institutes of Health. The plasma is pooled, irradiated to reduce the risk of homologous serum hepatitis, lyophilized, and sealed under vacuum. It is supplied desiccated in vacuum bottles to yield 50 cc., 250 cc., and 500 cc. of irradiated normal human plasma (or smaller quantities of *hypertonic* plasma).

Sharp & Dohme, Philadelphia 1, Pa.

*Whitelaw, M. J., J.A.M.A. *145:* 85, Jan. 13, 1951.